

3 Human Health Effects

3.1 Epidemiologic Considerations in Occupational Respiratory Disease Studies

3.1.1 Study Designs

Epidemiology is the study of patterns of disease occurrence in human populations and the factors that influence those patterns [Lilienfeld and Stolley 1994]. Epidemiology is the primary science used to study silica-related diseases in workers. Most epidemiologic studies of silica-exposed workers discussed in this review are cross-sectional studies (i.e., prevalence studies) or retrospective (i.e., historical) cohort studies. Cross-sectional studies measure symptom or disease occurrence in a selected population at one point in time. An example of a cross-sectional study design would be the spirometric testing of lung function in a group of granite shed workers during an annual

health survey and comparison with respiratory function in nongranite workers. Cross-sectional studies have two disadvantages:

- Usually only the “survivor” population is examined. Retired, former, or deceased workers are not included, possibly resulting in an underestimate of the disease prevalence.
- It may be impossible to determine whether exposure preceded the disease if both are measured at the same time.

Many epidemiologic studies of silica-related diseases are retrospective cohort morbidity or mortality studies. In this approach, the illnesses, deaths, and exposures (surrogate or reconstructed) of an entire cohort (e.g., all workers ever employed in one foundry) are followed forward from a time in the past to a



Photograph by Kenneth Linch, NIOSH

Construction workers drilling holes in concrete pavement during highway repair.

designated time in the future, and the number and causes of deaths that occur in that interval are assessed. Exposures for the followup period may be reconstructed from historical information or a surrogate measure such as duration of employment. The mortality of the cohort is then compared with the mortality of a standard population. For example, Steenland and Brown [1995b] used a retrospective study design to examine the mortality of a cohort of white male underground gold miners employed for at least 1 year between 1940 and 1965. The miners were followed from their first date of mining employment to their date of death or until the end of 1990, whichever came first. Their mortality was then compared with that of the U.S. population or the county where the mine was located. A disadvantage of silicosis mortality studies that use death certificate data is that silicosis cases could be underascertained even when contributing causes of death are included, as suggested by a study of silicosis mortality surveillance in the United States [Bang et al. 1995].

3.1.2 Sources of Bias

Three main (but not mutually exclusive) types of bias may affect the results of epidemiologic studies of silica-exposed workers—selection bias, information bias, and confounding [Checkoway 1995]:

- **Selection bias** originates from the method of choosing study subjects. This type of bias is a common criticism of lung cancer studies of compensated silicotics because silicotic workers who sought compensation for their disease may differ from all silicotics in symptoms, radiographic changes, social and psychological factors, and industry [Weill and McDonald 1996; McDonald 1995]. However, Goldsmith [1998] reviewed this question and concluded that lung cancer risk estimates were not

higher in compensated silicotics when compared with those of silicotics ascertained from other clinical sources (i.e., hospital or registry data).

- **Information bias** involves misclassification of study subjects by disease or exposure status [Checkoway et al. 1989]. An example of disease (silicosis) misclassification occurred in a study of North Carolina dusty trades workers [Amandus et al. 1991; Rice et al. 1986]: a re-evaluation of the chest X-rays found that 104 of the 370 cases categorized as silicosis were actually International Labour Organization (ILO) category 0 (nonsilicotic) [Amandus et al. 1992]. Sources of exposure assessment errors include instrument error, incorrect imputation of exposure when data are missing, and data extrapolation errors [Checkoway 1995]. Misclassification of exposure may occur in retrospective cohort studies of silicosis when quantitative dust exposure measurements are mathematically converted from particle counts to gravimetric respirable silica equivalents.

- **Confounding variables** are factors that are related to exposure and are also independent risk factors for the disease under study [Checkoway 1995]. Most studies of silica-related diseases controlled for confounding factors such as age and race by study design or data analysis. Confounding from cigarette smoking is an important concern in studies of lung cancer, bronchitis, asthma, emphysema, chronic obstructive pulmonary disease (COPD), and lung function. Confounding of an exposure-disease relationship by cigarette smoking is less likely when an internal comparison group is used—e.g., when both groups are from the same plant [Siemiatycki et al. 1988].

(Some studies in this review used external comparison populations.) Most of the lung cancer studies among underground miners did not control for the effects of other carcinogens that may have been present, such as arsenic, radon progeny, and diesel exhaust (see Section 3.4.1).

The effects of bias discussed here can be minimized by applying epidemiologic methods. Description of appropriate methodology is available in epidemiology textbooks.

3.2 Silicosis

3.2.1 Definition

Silicosis most commonly occurs as a diffuse nodular pulmonary fibrosis. This lung disease (which is sometimes asymptomatic [NIOSH 1996b]) is caused by the inhalation and deposition of respirable crystalline silica particles (i.e., particles <10 µm in diameter) [Ziskind et al. 1976; IARC 1987]. According to a report from the U.S. Surgeon General [DHHS 1985], cigarette smoking has “no significant causal role” in the etiology of silicosis. Probably the most important factor in the development of silicosis is the “dose” of respirable silica-containing dust in the workplace setting—that is, the product of the concentration of dust containing respirable silica in workplace air and the percentage of respirable silica in the total dust. Other important factors are (1) the particle size, (2) the crystalline or noncrystalline nature of the silica, (3) the duration of the dust exposure, and (4) the varying time period from first exposure to diagnosis (from several months to more than 30 years) [Banks 1996; Kreiss and Zhen 1996; Hnizdo and Sluis-Cremer 1993; Hnizdo et al. 1993; Steenland and Brown 1995a; ATS 1997]. Experimental evidence supporting the influence of these factors has recently been reviewed [Mossman and Churg 1998; Heppleston 1994]. Many in vitro studies have been

conducted to investigate the surface characteristics of crystalline silica particles and their influence on fibrogenic activity [Bolsaitis and Wallace 1996; Fubini 1997, 1998; Castranova et al. 1996; Donaldson and Borm 1998; Erdogan and Hasirci 1998]. These researchers found that a number of features may be related to silica cytotoxicity. Further research is needed to associate the surface characteristics with occupational exposure situations and health effects [Donaldson and Borm 1998]. Such exposure situations may include work processes that produce freshly fractured silica surfaces [Bolsaitis and Wallace 1996; Vallyathan et al. 1995] or that involve quartz contaminated with trace elements such as iron [Castranova et al. 1997].

A worker may develop one of three types of silicosis, depending on the airborne concentration of respirable crystalline silica: (1) chronic silicosis, which usually occurs after 10 or more years of exposure at relatively low concentrations; (2) accelerated silicosis, which develops 5 to 10 years after the first exposure; or (3) acute silicosis, which develops after exposure to high concentrations of respirable crystalline silica and results in symptoms within a period ranging from a few weeks to 5 years after the initial exposure [NIOSH 1996b; Parker and Wagner 1998; Ziskind et al. 1976; Peters 1986]. The symptoms of accelerated silicosis are similar to those of chronic silicosis, but clinical and radiographic progression is rapid. Also, fibrosis may be irregular and more diffuse [Banks 1996; Seaton 1995; Silicosis and Silicate Disease Committee 1988] or not apparent on the chest radiograph [Abraham and Weisenfeld 1997]. Acute silicosis is typically associated with a history of high exposures from tasks that produce small particles of airborne dust with a high silica content, such as sandblasting, rock drilling, or quartz milling [Davis 1996]. The pathologic characteristics of acute silicosis (sometimes referred to as silicoproteinosis) resemble those of alveolar proteinosis [Wagner 1994; Davis 1996].

Pulmonary fibrosis may not be present in acute silicosis [NIOSH 1996b].

Epidemiologic studies of gold miners in South Africa, granite quarry workers in Hong Kong, metal miners in Colorado, and coal miners in Scotland have shown that chronic silicosis may develop or progress even after occupational exposure to silica has been discontinued [Hessel et al. 1988; Hnizdo and Sluis-Cremer 1993; Hnizdo and Murray 1998; Ng et al. 1987; Kreiss and Zhen 1996; Miller et al. 1998]. Therefore, removing a worker from exposure after diagnosis does not guarantee that silicosis or silica-related disease will stop progressing or that an impaired worker's condition will stabilize [Parker and Wagner 1998; Weber and Banks 1994; Wagner 1994].

3.2.2 Epidemiologic Exposure-Response Models of Silicosis

This section reviews published epidemiologic studies that provide evidence of an exposure-response relationship for crystalline silica and silicosis using cumulative exposure data. Exposure-response models based on cumulative exposure data can predict silicosis risk for a particular silica dust exposure over a period of time. Epidemiologic studies that provided evidence of an exposure-response relationship for silica and silicosis on the basis of other kinds of exposure data (e.g., duration of exposure) have been reviewed elsewhere [EPA 1996; Davis 1996; Hughes 1995; Rice and Stayner 1995; Seaton 1995; Steenland and Brown 1995a; Goldsmith 1994a; WHO 1986].

Table 12 summarizes the published studies that predict the incidence or prevalence of radiographic silicosis based on models of cumulative exposure to respirable crystalline silica. Table 13 presents details about the cohorts, quartz content of the dust, followup periods, and limitations of each study. All of the studies

predicted the occurrence of at least one case of radiographic silicosis per 100 workers at cumulative exposures approximately equal to the OSHA and MSHA PELs and the NIOSH REL over a 40- or 45-year working lifetime (see appendix for the PELs and REL). Three studies predicted prevalences of 47% to 95% at the OSHA PEL. Each study followed a cohort of miners for at least three decades from first employment in the industry [Kreiss and Zhen 1996; Hnizdo and Sluis-Cremer 1993; Steenland and Brown 1995a]. Studies of foundry workers [Rosenman et al. 1996], hardrock miners [Muir et al. 1989a,b; Muir 1991], and workers in the diatomaceous earth industry [Hughes et al. 1998] followed workers for less than 30 years (mean) and predicted prevalences of 1% to 3%. The studies presented in Table 12 predicted that approximately 1 to 7 silicosis cases per 100 workers would occur at respirable quartz concentrations of 0.025 mg/m^3 —half the NIOSH REL of 0.05 mg/m^3 —with the contingencies and exceptions noted in Table 12. However, that concentration cannot be measured accurately at this time for the reasons given in Section 2.4.

Table 12 does not include a cohort study of 1,416 coal miners exposed to coal dust with quartz concentrations ranging from 0.4% to 29.4% of respirable dust [Miller et al. 1998]. This study predicted pneumoconiosis risks for 47 men with a “profusion of median small opacities” of ILO category $\geq 2/1$ (i.e., 2/1+), a higher category of radiographic abnormality than reported in the studies listed in Tables 12 and 13. Logistic regression models predicted that the risk of small opacities of 2/1+ at the time of followup examination would be about 5% for miners exposed to a mean respirable quartz concentration of 0.1 mg/m^3 and about 2% for miners exposed to a mean respirable quartz concentration of 0.05 mg/m^3 for about 15 years [Miller et al. 1998]. The predicted risks increased with cumulative exposure to respirable quartz dust.

Table 12. Predicted incidence or prevalence of silicosis following exposure to selected concentrations of respirable quartz dust—based on modeling of cumulative exposure over a 45-year working lifetime

Study and cohort	Selected mean concentration of respirable quartz dust (mg/m ³)	Mean time since first quartz exposure (yr)	Maximum time since first quartz exposure (yr)	Predicted incidence or prevalence of silicosis, ILO category $\geq 1/1$ (cases/100 workers)
Hnizdo and Sluis-Cremer [1993], 2,235 South African gold miners	0.05 0.10	36* —	50*	13† 70‡
Hughes et al. [1998], 2,342 U.S. workers in a diatomaceous earth mining and processing facility	0.05 0.10	11.5 —	46	1.5§–4*,** 4§–17†,**
Kreiss and Zhen [1996], 100 U.S. hardrock miners and 34 community controls	0.05 0.10	41.6* 33.5**	66* 68**	30†,†† 90†,††
Muir et al. [1989a,b] and Muir [1991], 2,109 Canadian gold and uranium miners	0.05	18	38*	0.09–0.62§§
Ng and Chan [1994], 338 Hong Kong granite workers	0.045†,***	—†††	—	6
Rosenman et al. [1996], 1,072 U.S. gray iron foundry workers	0.05 0.10	28 —	>30	2**** 3****
Steenland and Brown [1995a], 3,330 U.S. gold miners	0.05 0.09	37 —	73 §§§	10**** 47****

*Silicotic miners.

†Estimate reported in Rice and Stayner [1995].

‡Approximate.

§Primarily cristobalite dust. Cumulative risk of small opacities \geq ILO category 1/0 and/or large opacities. For 1,452 workers with an average crystalline silica exposure ≤ 0.50 mg/m³; 1,138 (78%) of these workers were hired in 1950 or later.

**Primarily cristobalite dust. Cumulative risk of small opacities \geq ILO category 1/0 and/or large opacities. For 357 workers with an average crystalline silica exposure >0.50 mg/m³; 319 (89%) of these workers were hired before 1950.

†Based on cumulative silica exposure model with 10 yr of post-employment followup.

‡Nonsilicotic miners.

§§No post-employment followup and no retired miners included. The range includes five estimates (one for each reader). Estimate reported in Rice and Stayner [1995].

**Based on a 50-year-old worker with cumulative silica exposure of 2 mg/m³ yr.

†††Not reported. Mean duration of employment was 17 yr for all workers and 27.5 yr for workers in the highest category of cumulative silica exposure.

§§§Steenland [1998].

****Includes 141 cases documented on death certificate only. Estimated risk not adjusted for age or calendar time [Steenland 1997].

Table 13. Summary of epidemiologic studies of silicosis with cumulative dust exposure data and silicosis risk estimates

Reference, country, and study design	Cohort	Definition of silicosis, mean duration of employment, and mean yr since first quartz exposure	Silica (quartz) content of respirable dust	Measure of association	Comments
Hnizdo and Sluis-Cremer [1993], South Africa, cohort study	2,235 white underground gold miners who were aged 45 to 54 at time of medical examination in 1968–1971, started working after 1938, worked ≥ 10 yr, and were followed until 1991.	ILO* category $\geq 1/1$ and rounded opacities (313 cases); 23.5 yr for total cohort and 26.9 yr for cases; 36 yr for cases.	30% after heat and acid treatment [Beadle and Bradley 1970].	Cumulative risk	Authors speculated that these silicosis risk estimates were higher than estimates for Canadian miners reported by Muir et al. [1989a,b] and Muir [1991] because (1) dust exposure may have been underestimated, (2) South African gold mine dust may be more fibrogenic than Canadian mine dust, (3) average proportion of quartz may be $>30\%$, (4) there may have been differences in age at end of radiological follow-up, and (5) exposures for Canadian miners (Hnizdo's [1995] response to Hughes and Weill [1995]) may have been overestimated.

See footnotes at end of table.

Table 13 (Continued). Summary of epidemiologic studies of silicosis with cumulative dust exposure data and silicosis risk estimates

Reference, country, and study design	Cohort	Definition of silicosis, mean duration of employment, and mean yr since first quartz exposure	Silica (quartz) content of respirable dust	Measure of association	Comments
Hughes et al. [1998], United States, retro- spective cohort study	2,342 white male workers employed at least 1 yr between 1942 and 1987 in one diatomaceous mining and processing facility. Exposure-response analy- ses included the 1,809 men with a radiograph taken more than 1 month after hire.	Small opacities \geq ILO profusion category 1/0 and/or large opacities (81 cases), 5.54 yr [†] , 11.5 yr.	Natural diatomite, 3%; calcined diatomite, 20%; flux-calcined diatomite, 60% (see comments).	Cumulative risk	82 workers had radiographs taken after retirement—development of opacities was not recorded for other workers after they left employ- ment. Quantitative air-monitoring data were available after 1948; respirable dust concentrations be- fore 1948 were estimated [Seixas et al. 1997]. Cumulative risk esti- mates for radiographic opacities were lower for workers who were hired after 1950 and who had lower average exposures to crystalline silica dust (mainly cristobalite). Estimated percentages of respirable crystalline silica reported by Checkoway et al. [1997] in mortality study of same cohort: 10% for calcined diatomaceous earth, and 20% for flux-calcined diatomaceous earth.

See footnotes at end of table.

(Continued)

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Reference, country, and study design	Cohort	Definition of silicosis, mean duration of employment, and mean yr since first quartz exposure	Silica (quartz) content of respirable dust	Measure of association	Comments
Kreiss and Zhen [1996], United States, community-based random sample survey	134 male residents of a hardrock [‡] mining town who were aged ≥40: 100 silica-exposed hardrock miners (included 32 silicosis cases) and 34 community controls without occupational dust exposure.	ILO category ≥ 1/0; 27.6 yr for silicotics and 22.9 yr for nonsilicotic miners; 41.6 yr for silicotics and 33.5 yr for nonsilicotics.	12.3%	Prevalence	Possible overestimation of silicosis risk because of underestimation of pre-1974 dust and silica exposures. Exposures were also estimated for mines where there were no exposure data (17.1% of the person-yr of followup).

Risk estimates were presented for models of cumulative silica dust exposure or cumulative dust exposure—the models of cumulative silica dust exposure gave higher estimates. Silicosis (i.e., ≥ category 1/1) risk estimates from models of cumulative dust exposure were similar to estimates for South African gold miners [Hnizdo and Sluis-Cremer 1993] and U.S. gold miners [Steenland and Brown 1995a].

See footnotes at end of table.

Table 13 (Continued). Summary of epidemiologic studies of silicosis with cumulative dust exposure data and silicosis risk estimates

Reference, country, and study design	Cohort	Definition of silicosis, mean duration of employment, and mean yr since first quartz exposure	Silica (quartz) content of respirable dust	Measure of association	Comments
Muir et al. [1989a,b], Verma et al. [1989], Muir [1991]; Canada; retrospective cohort study	2,109 current Ontario gold and uranium miners who started and worked ≥ 5 yr between 1940 and 1959 and were followed to 1982 or to the end of their dust exposure, whichever came first.	ILO category $\geq 1/1$ and small, rounded opacities (32 cases); approximately 20 yr; approximately 25 yr (based on interpre- tation of data in table and graph of Muir et al. [1989b]).	6.0% for gold mine dust; 8.4% for uranium mine dust.	Cumulative risk	Retired and former workers not included, which may have under- estimated silicosis risk. Disagree- ment about silicosis classification among the five readers of the chest X-rays may have “complicated the analysis” [Muir et al. 1989b].

See footnotes at end of table.

Table 13 (Continued). Summary of epidemiologic studies of silicosis with cumulative dust exposure data and silicosis risk estimates

Reference, country, and study design	Cohort	Definition of silicosis, mean duration of employment, and mean yr since first quartz exposure	Silica (quartz) content of respirable dust	Measure of association	Comments
Ng and Chan [1994], Hong Kong, cross- sectional study	338 current and previous granite workers employed ≥ 1 yr between 1967 and 1985.	ILO category $\geq 1/1$ (rounded or irregular opacities); 17.4 yr; not reported.	27%	Prevalence	Cumulative risks not calculated. Exposure data for 1976–1981 in one quarry and for 1971–1975 and 1976–1981 in another quarry were not available and were assumed to be the same concentrations measured in 1982 for the period 1976–1981 and in 1971 for the period 1971–1985 [Ng et al. 1987]. Possible under- estimate of silicosis risk because decedents were not included.

See footnotes at end of table.

Table 13 (Continued). Summary of epidemiologic studies of silicosis with cumulative dust exposure data and silicosis risk estimates

Reference, country, and study design	Cohort	Definition of silicosis, mean duration of employment, and mean yr since first quartz exposure	Silica (quartz) content of respirable dust	Measure of association	Comments
Rosenman et al. [1996], United States, cross- sectional study	549 current, 497 retired, and 26 current salaried workers that were former production workers in a gray iron foundry that pro- duced automotive engine blocks (total workers=1,072).	ILO category $\geq 1/0$ and rounded opacities (28 cases); 19.2 yr; 28.3 yr.	Not reported.	Prevalence	Prevalence of silicosis cases increased with (1) years of employment, (2) cigarette smoking, (3) mean silica exposure, and (4) cumulative silica exposure. Exposure estimates were derived from conversions of “early silica exposure data” collected by impin- gers. Underascertainment of sili- cosis cases is likely because there was no systematic radiologic fol- lowup of retired workers. Results showed that African-American workers had two times the risk of radiographic silicosis compared with white workers but a similar duration of employment; however, African-American workers had greater mean exposure to silica dust. When exposure to silica was controlled for in the analysis, the prevalence of radiographic silicosis was similar for African-American workers and white workers.

See footnotes at end of table.

Table 13 (Continued). Summary of epidemiologic studies of silicosis with cumulative dust exposure data and silicosis risk estimates

Reference, country, and study design	Cohort	Definition of silicosis, mean duration of employment, and mean yr since first quartz exposure	Silica (quartz) content of respirable dust	Measure of association	Comments
Steenland and Brown [1995a], United States, cohort study	3,330 white male underground gold miners employed ≥ 1 yr between 1940 and 1965 and followed through 1990.	Mortality [§] and ILO category $\geq 1/1$ (1976 radiographic survey) or “small opacities” or “large opacities” (1960 radiographic survey) (170 cases); 9 yr; 37 yr.	13% [Zumwald et al. 1981]	Cumulative risk	Silicosis risk estimates could have been affected by (1) combining silicosis deaths with silicosis cases detected by cross-sectional radiographic surveys, (2) difference in quartz content of dust in early years, (3) lack of dust measurements before 1937.

^{*}International Labour Organization.[†]Median [Checkoway et al. 1997].[‡]Molybdenum, lead, zinc, and gold mining.[§]Underlying or contributing cause of death was silicosis, silico-tuberculosis, respiratory tuberculosis, or pneumoconiosis.

A currently unpublished study of 600 retired Vermont granite workers found nodular opacities consistent with silicosis (degrees of profusion not reported in abstract) in 4.7% of 360 radiographs read by three readers [Graham et al. 1998]. The average duration of employment for these workers was 31 years, and the average time from first exposure to radiographic examination was 39 years. Most workers in the cohort were first employed after 1940, when average quartz dust concentrations were below the current OSHA PEL [Graham et al. 1991; Ashe and Bergstrom 1964].

Although the variability in prevalence estimates (i.e., 1% to 90%) cannot be solely attributed to differences in followup periods, chronic silicosis is a progressive disease, and its development after a long latency period and after workers leave employment must be accounted for in epidemiologic studies. A study of autopsied gold miners in South Africa also supports the need for examining workers after a long latency period and after they leave employment [Hnizdo et al. 1993]. Radiologic findings for profusion of rounded opacities (ILO category $\geq 1/1$) were compared with pathological findings for silicosis in 326 miners with an average of 2.7 years between the radiologic and pathologic examinations. Silicosis was not diagnosed radiographically for at least 61% of the miners with slight to marked silicosis at autopsy. The probability of a false negative reading increased with years of mining and average concentration of respirable dust [Hnizdo et al. 1993]. Experimental studies of rats also reported a lack of complete agreement between histopathologic indicators of silica dust exposure and radiographic readings [Drew and Kutzman 1984a,b].

In addition, improved exposure assessment methods and data analyses that account for variations and deficiencies in exposure data would improve the risk estimates for silica-exposed workers [Agius et al. 1992; Checkoway

1995]. Although epidemiologic studies that used cumulative exposure estimates represent the best available source of information for characterizing the dose-response relationship in occupational cohorts, peak exposures may predict silicosis risk better than cumulative exposures [Checkoway and Rice 1992]. However, data on peak exposures are rarely available, and data supporting this hypothesis are limited.

3.3 TB and Other Infections

3.3.1 Definition

As silicosis progresses, it may be complicated by severe mycobacterial or fungal infections [NIOSH 1996b; Ziskind et al. 1976; Parkes 1982; Parker 1994]. The most common of these infections, TB, occurs when the macrophages are overwhelmed by silica dust and are unable to kill the infectious organism *Mycobacterium tuberculosis* [Parker 1994; Ng and Chan 1991; NIOSH 1992a,b; Allison and Hart 1968]. About half of the mycobacterial infections that occur in workers with exposure to silica are caused by *M. tuberculosis*, and the other half are caused by the nontuberculous mycobacteria (NTM) *Mycobacterium kansasii* and *Mycobacterium avium-intracellularare* [Owens et al. 1988; NIOSH 1996b]. Infections in workers with silicosis may also be caused by *Nocardia asteroides* and *Cryptococcus* [Ziskind et al. 1976; NIOSH 1996b; Parker 1994; Parker and Wagner 1998]. ATS [1997] recommends that the diagnostic investigation of a patient with silicosis and possible TB include consideration of NTM disease. The ATS also recommends that tuberculin tests be administered to persons with silicosis and to those without silicosis who have at least 25 years of occupational exposure to crystalline silica [ATS 1997].

3.3.2 Epidemiologic Studies

Recent surveillance data indicate that TB rates in the United States are 5 to 10 times higher

among racial and ethnic minorities (after adjustment for the effects of age, sex, and country of birth) [Cantwell et al. 1998]. Cantwell et al. [1998] reported that the relative risk of TB increased as socioeconomic status (measured by six indicators) decreased, after adjustment for the effects of age (relative risks ranged from 2.6 to 5.6 in the lowest versus highest quartiles). The number of TB cases among foreign-born persons in the United States increased by 56% during the period 1986 to 1997 [CDC 1998c].

The association between TB and silicosis has been firmly established by the results of epidemiologic studies conducted during this century [Balmes 1990]. This association was supported by a survey of TB deaths among silicotics in the United States for the period 1979 to 1991 [Althouse et al. 1995] and by the results of four recent epidemiologic studies [Goldsmith et al. 1995; Cowie 1994; Sherson and Lander 1990; Kleinschmidt and Churchyard 1997]. Black South African gold miners [Cowie 1994] and Danish foundry workers [Sherson and Lander 1990] with chronic silicosis had threefold and tenfold incidences of TB, respectively, compared with nonsilicotic, non-silica-exposed workers of similar age and race. Goldsmith et al. [1995] compared the mortality of 590 California silicosis claimants with that of U.S. males and found that the TB mortality of the claimants was 50 times that of all U.S. males (standardized mortality ratio [SMR]=56.35; 45 deaths observed, 0.8 expected; 95% confidence interval [CI]=41.10–75.40). A retrospective study of TB among 4,976 miners from the Freegold mines in South Africa reported that the incidence rate ratio for miners with silicosis (ILO category $\geq 1/1$) was 1.54 (95% CI=1.00–2.37) compared with miners without silicosis (after adjusting for the effects of age, followup period, cumulative service, and occupation) [Kleinschmidt and Churchyard 1997]. The incidence of TB for the oldest age group was 21 times that of the youngest group (incidence rate ratio=21.17;

95% CI=8.60–52.11); and for workers in occupations with high dust exposure (such as drilling), the incidence was twice that of surface and maintenance workers (adjusted incidence rate ratio=2.25; 95% CI=1.49–3.38) [Kleinschmidt and Churchyard 1997].

Some evidence indicates that workers who do not have silicosis but who have had long exposures to silica dust may be at increased risk of developing TB. Two epidemiologic studies reported that, compared with the general population, a threefold incidence of TB cases occurred among 5,424 nonsilicotic, silica-exposed Danish foundry workers employed 25 or more years [Sherson and Lander 1990], and nearly a tenfold incidence occurred among 335 nonsilicotic, black South African gold miners with a median underground employment of 26 years [Cowie 1994].

Westerholm et al. [1986] found 13 cases among 428 silicotic Swedish iron and steel workers and 1 case in a comparison group of 476 Swedish iron and steel workers with normal chest radiographs (level of statistical significance not reported). Both groups had been exposed to silica for at least 5 years.

A study of TB incidence in 2,255 white South African gold miners included 1,296 miners who had an autopsy [Hnizdo and Murray 1998, 1999]. The smoking-adjusted relative risk for TB in miners without silicotic nodules on autopsy examination ($n=577$) increased slightly with quartiles of cumulative dust exposure (relative risk=1.38 [95% CI=0.33–5.62] for the highest quartile of cumulative exposure). For miners without radiologically diagnosed silicosis ($n=1,934$), the smoking-adjusted relative risk increased to 4.01 (95% CI=2.04–7.88) in the highest quartile of cumulative dust exposure [Hnizdo and Murray 1998, 1999]. The authors defined radiologic silicosis as ILO category $\geq 1/1$. TB was diagnosed, on the average, 7.6 years after the end of dust exposure and

6.8 years after the onset of radiological silicosis—a result that supports the need for medical surveillance of workers after the end of exposure to silica dust [Hnizdo and Murray 1998]. Miners who developed TB before completing 10 years of underground employment were excluded because they were not allowed to continue working underground after diagnosis.

Corbett et al. [1999] conducted a recent case-control study of TB and pulmonary disease caused by NTM in South African gold miners. These researchers found that radiographic silicosis, focal radiological scarring, and human immunodeficiency virus (HIV) infection were significant risk factors for NTM disease and for TB. Past medical history of TB treatment (odds ratio [OR]=15.1; 95% CI=7.64–29.93) and current employment in a “dusty job” at the mines (OR=2.5; 95% CI=1.46–4.44) were significant risk factors for NTM. ORs for NTM and TB increased with years of employment (range of ORs was 1.0 to 9.4 for NTM and 1.0 to 4.1 for TB). The study included 206 NTM patients and 381 TB patients of known HIV status admitted to a South African hospital. Also included were 180 controls who were HIV-tested surgical or trauma patients admitted to the same hospital during the same period.

Two recent studies about silica exposure and TB used U.S. occupational mortality data to conduct a proportionate mortality study of persons with TB by occupation for 1979 through 1990 [CDC 1995; Chen et al. 1997]. Although the study design did not control for confounding, it identified six occupational groups with potential exposure to silica dust that had age-adjusted proportionate mortality ratios (PMRs) for TB that were statistically significant (lower bound of the 95% CI>100) or greater than 200. Table 14 shows significant PMRs by race for construction occupations, mining machine operators, grinding and polishing machine operators, furnace and kiln

operators, laborers, and mixing and blending machine operators [CDC 1995].

Chen et al. [1997] conducted a case-control study (8,740 cases; 83,338 controls) with U.S. National Occupational Mortality Surveillance (NOMS) data for 1983–1992. The study controlled for confounding from age, sex, race, socioeconomic status, potential exposure to active TB, and the presence of silicosis and other pneumoconioses. The potential for silica exposure was based on data from NOES [NIOSH 1988] and the National Occupational Health Survey of Mining (NOHSM) [NIOSH 1996c]. This potential was categorized as “high,” “intermediate,” or “low or no.” The study found that decedents with high potential for exposure to silica and no documentation of silicosis on the death certificate had a 30% greater odds of mortality from respiratory TB than decedents with no potential exposure to silica after adjustment by logistic regression for the possible confounders mentioned earlier (OR=1.3; 95% CI=1.14–1.48). The results also suggest an exposure-response relationship between silica exposure (in the absence of silicosis) and death from respiratory tuberculosis [Chen et al. 1997].

3.4 Cancer

3.4.1 Background

The possible carcinogenicity of crystalline silica dust became a subject of considerable and intense debate in the scientific community in the 1980s, especially after (1) publication of new information presented at a 1984 symposium in North Carolina [Goldsmith et al. 1986], (2) epidemiologic studies by Westerholm [1980] and Finkelstein et al. [1982], and (3) a literature review by Goldsmith et al. [1982] (see McDonald [1989, 1995] and Graham [1998]). Many epidemiologic studies of cancer mortality and morbidity in silica-exposed occupational groups were published

Table 14. Selected age-adjusted PMRs^{a,b} for pulmonary TB by usual occupation, sex, and race in 28 States, 1979–1990

Occupation of decedent and 1980 census code	Male decedents						Female decedents					
	White			Black			White			Black		
	Number	PMR	95% CI	Number	PMR	95% CI	Number	PMR	95% CI	Number	PMR	95% CI
Construction occupations (553–599, 865, and 869)	169	134 [†]	114–156	105	128 [†]	104–155	0	—	—	0	—	—
Brick and stone mason (553 and 563–564)	12	213 [†]	110–371	11	159	80–285	0	—	—	0	—	—
Carpenter (554, 567, and 569)	50	147 [†]	109–194	9	97	44–184	0	—	—	0	—	—
Roofer (595)	6	290 [†]	106–630	1	53	1–293	0	—	—	0	—	—
Construction laborer (869)	34	175 [†]	121–244	61	156 [†]	120–201	0	—	—	0	—	—
Mining machine operator (616)	54	276 [†]	207–360	4	128	35–328	0	—	—	0	—	—
Grinding, abrading, buffing, or polishing machine operator (709)	7	265 [†]	107–547	1	94	2–523	0	—	—	0	—	—
Mixing or blending machine operator (756)	1	58	2–326	5	376 [†]	122–878	0	—	—	0	—	—
Furnace, kiln, or oven operator, except food (766)	1	27	1–153	5	206 [†]	67–481	0	—	—	1	15,00	372–82,842
Laborer, except construction (889)	85	159 [†]	127–196	92	111	89–136	12	162	84–283	8	147	64–291

Source: Adapted from CDC [1995]. This data file includes death records from 28 States (Alaska, California, Colorado, Georgia, Idaho, Indiana, Kansas, Kentucky, Maine, Missouri, Nebraska, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Carolina, Ohio, Oklahoma, Pennsylvania, Rhode Island, South Carolina, Tennessee, Utah, Vermont, Washington, West Virginia, and Wisconsin).

^aAbbreviations: PMRs = proportionate mortality ratios; TB = tuberculosis; CI = confidence interval.

^bSelection criteria: (1) at least four TB deaths in race- and sex-specific group and (2) either a PMR >200 or a PMR with a 95% CI excluding 100.

later, but the issue remained unresolved. In October 1996, an IARC expert working group reviewed the published experimental and epidemiologic studies of cancer in animals and workers exposed to respirable crystalline silica. The working group concluded that there is “sufficient evidence in humans for the carcinogenicity of inhaled crystalline silica in the form of quartz or cristobalite from occupational sources” [IARC 1997]. In June 1996, the directors of the ATS adopted an official statement of their Committee of the Scientific Assembly on Environmental and Occupational Health. This statement, prepared at the request of the American Lung Association Occupational Health Expert Advisory Group [ATS 1997], described the adverse health effects of exposure to crystalline silica, including lung cancer. The ATS found the following:

- The available data support the conclusion that silicosis produces increased risk for bronchogenic carcinoma.
- However, less information is available for lung cancer risk among silicotics who never smoked and workers who were exposed to silica but did not have silicosis.
- Whether silica exposure is associated with lung cancer in the absence of silicosis is less clear.

NIOSH concurs with the conclusions of the IARC working group and the ATS. These conclusions agree with NIOSH testimony to OSHA, in which NIOSH recommended that crystalline silica be considered a potential occupational carcinogen [54 Fed. Reg. 2521 (1989)].

This section, like the IARC review, focuses on lung cancer and discusses the epidemiologic studies that were the least likely to have results affected by confounding and selection biases.

In “mixed” environments such as ceramics, pottery, or brick manufacturing, where exposure may be to two or more polymorphs of crystalline silica, epidemiologic studies have usually not identified specific exposures to quartz or cristobalite. Therefore, excess lung cancers that occurred in these environments cannot be associated with exposure to a given polymorph but only with exposure to respirable crystalline silica. The epidemiologic studies of cancer have mainly investigated workers exposed to respirable crystalline silica in (1) ore mining, (2) quarrying and granite works, (3) ceramics, pottery, glass, refractory brick, and diatomaceous earth industries, or (4) foundries. The other major study group was workers with silicosis, usually identified from national or local registries. Studies of workers and silicotics that were not discussed in this document because they failed to meet the “least confounded” criterion have been criticized for the following reasons [Checkoway 1995; McDonald 1995, 1996; Morgan and Reger 1995; Weill and McDonald 1996; Seaton 1995; Weill et al. 1994; Agius et al. 1992]:

- Inadequate, incomplete, or invalid exposure assessment
- Potential selection and confounding biases in the cohort studies of compensated silicotics
- Inadequate control of confounding from cigarette smoking and from concurrent workplace exposures (e.g., potential exposure to radon progeny, arsenic, or diesel exhaust in ore mines and potential exposure to polycyclic aromatic hydrocarbons in foundries)
- Inability to distinguish differences in fibrogenic and carcinogenic potencies of the various silica polymorphs
- Lack of evidence of an exposure-response relationship

3.4.2 Epidemiologic Studies of Lung Cancer

Following a comprehensive review of the large body of published epidemiologic studies, IARC [1997] found that the following studies provide the least confounded investigations of an association between occupational exposure to crystalline silica and lung cancer:

1. U.S. gold miners [Steenland and Brown 1995b]
2. Danish stone industry workers [Guénél et al. 1989]
3. U.S. granite shed and quarry workers [Costello and Graham 1988]
4. U.S. crushed stone industry workers [Costello et al. 1995]
5. U.S. diatomaceous earth industry workers [Checkoway et al. 1993, 1996]
6. Chinese refractory brick workers [Dong et al. 1995]
7. Italian refractory brick workers [Merlo et al. 1991; Puntoni et al. 1988]
8. U.K. pottery workers [McDonald et al. 1995, 1997; Cherry et al. 1995, 1997; Burgess et al. 1997]
9. Chinese pottery workers [McLaughlin et al. 1992]
10. Cohorts of registered silicotics from North Carolina [Amandus et al. 1991, 1992] and Finland [Kurppa et al. 1986; Partanen et al. 1994]

Although a few of these studies did not find a statistically significant association between occupational exposure to crystalline silica and lung cancer (Table 15), most of the studies did.

Study results are often not uniform when a large number of epidemiologic studies are reviewed and a variety of populations and work environments are studied [IARC 1997]. In addition, IARC noted that the carcinogenicity of quartz or cristobalite “may be dependent on inherent characteristics of the crystalline silica or on external factors affecting its biological activity or distribution of its polymorphs” [IARC 1997].

Some of the least confounded studies reported that lung cancer risk tended to increase with

- cumulative exposure to respirable silica [i.e., Checkoway et al. 1993, 1996],
- duration of exposure [i.e., Merlo et al. 1991; Partanen et al. 1994; Costello and Graham 1988; Costello et al. 1995; Dong et al. 1995],
- peak intensity of exposure [Burgess et al. 1997; Cherry et al. 1997; McDonald et al. 1997],
- the presence of radiographically defined silicosis [Amandus et al. 1992; Dong et al. 1995], and
- length of followup time from date of silicosis diagnosis [Partanen et al. 1994] (see Table 15).

These observed associations, including the exposure-response associations, are unlikely to be explained by confounding or other biases. Thus overall, the epidemiologic studies support increased lung cancer risks from occupational exposure to inhaled crystalline silica (i.e., quartz and cristobalite) [IARC 1997].

3.4.2.1 Updated or New Studies Since the IARC Review

Two studies discussed in this section have recently been updated: Checkoway et al. [1997, 1999] updated their previous mortality studies

Table 15. IARC^{*}-reviewed epidemiologic studies having the least confounded investigations of an association between occupational exposure to crystalline silica and lung cancer

Reference and country	Study design, cohort, and followup	Subgroup	Number of lung cancer deaths or cases	Risk measure [†]	CI [‡]	Smoking information available and analyzed	Comments
Amandus et al. [1991], United States	Mortality study of 714 male, North Carolina dusty trades workers diagnosed with silicosis between 1940 and 1983 and compared with the 1940–1983 lung cancer mortality rates for U.S. males.	Whites Nonwhites	33 1	2.6 0.7	1.8–3.6	Yes	The age- and smoking-adjusted rate ratio for white silicotics with lung cancer was 3.9 (95% CI= 2.4–6.4) compared with a referent group of metal miners.
	White silicotics: Diagnosed while employed	28		2.5	1.7–3.7		
	Employed in jobs with silica exposure only [§]	26		2.3	1.5–3.4		
	Past or current smokers	18		3.4	2.0–5.3		
	Silicotics, never smoked	5		1.7	0.5–3.9		No quantitative exposure data were available.
	Silicotics Nonsilicotics ^{**}	8 2		2.5 1.0	1.1–4.9 0.1–3.5	Yes	"Exposure to respirable silica dust" was defined as working in a dusty trade and having radiographic silicosis.
Amandus et al. [1992], United States	Mortality study of subgroup of 306 white males from Amandus et al. [1991] cohort of silicotics diagnosed and traced from 1940 through 1983. 143 of the subgroup were reclassified as silicotics, and 96 were reclassified as having a normal radiograph. 10 deaths from lung cancer occurred in the reclassified group.	Smokers: Silicotics Nonsilicotics ^{**}	5 1	3.4 1.3	1.1–7.9 0.03–7.1	No quantitative exposure data were available.	

See footnotes at end of table.

(Continued)

Table 15 (Continued). IARC^{*}-reviewed epidemiologic studies having the least confounded investigations of an association between occupational exposure to crystalline silica and lung cancer

Reference and country	Study design, cohort, and followup	Subgroup	Number of lung cancer deaths or cases	Risk measure [†]	CI [‡]	Comments	Smoking information available and analyzed
Burgess et al. [1997], Cherry et al. [1997], McDonald et al. [1997], United Kingdom	Nested case-control study of lung cancer deaths within Cherry et al. [1995], including duration and intensity of exposure, smoking, and radiological changes. Cases were employed as pottery workers for ≥10 yr. Each death was matched with 3 or 4 controls on date of birth and date of first exposure.	Cumulative exposure to respirable crystalline silica dust ≥4,000 µg/m ³ ·yr Duration of employment ≥20 yr Mean intensity of silica dust exposure ≥200 µg/m ³ Maximum silica dust exposure ≥400 µg/m ³	52 — — —	0.60 ^{††} 0.48 ^{††} 1.68 ^{††} 2.07 ^{††}	0.26–1.41 ^{‡‡} 0.21–1.09 ^{‡‡} 0.93–3.03 ^{‡‡} 1.04–4.14 ^{‡‡}	Yes This was the only epidemiologic study of peak exposure effects and lung cancer. Results support significant lung cancer risk for high-intensity silica exposures. Silica dust exposures ≥400 µg/m ³ occurred in firing and post-firing operations. Exposures to cristobalite were possible.	ORs were adjusted for smoking and radiographic changes.

See footnotes at end of table.

(Continued)

Table 15 (Continued). IARC^{*}-reviewed epidemiologic studies having the least confounded investigations of an association between occupational exposure to crystalline silica and lung cancer

Reference and country	Study design, cohort, and followup	Subgroup	Number of lung cancer deaths or cases	Risk measure [†]	CI [‡]	Comments	Smoking information available and analyzed
Checkoway et al. [1993; 1996], United States	Mortality study of 2,570 male workers at diatomaceous earth plants employed ≥ 1 yr and worked ≥ 1 day between 1942 and 1987. Cohort mortality traced for that period.	—	59	1.43	1.09–1.84	Limited to comparisons of smoking prevalence.	Estimated relative risks for lung cancer (not shown) were adjusted for age, calendar year, duration of followup, and ethnicity. The risks increased significantly ($P \leq 0.05$ for trend) with duration of employment and cumulative exposure to crystalline silica [Checkoway et al. 1993]. Checkoway et al. [1996] also adjusted for asbestos exposure.
Checkoway et al. [1996]	—	52	1.41	1.05–1.85			
Checkoway et al. [1996]	reanalyzed 2,266 workers (a subset of the original cohort). Mortality traced from 1942 through 1987.	—					
Cherry et al. [1995], United Kingdom	Mortality study of 5,115 pottery workers, excluding exposure to asbestos, foundry, and other dusts; with mortality followup to June 30, 1992.	—	68	1.28	1.04–1.57 [‡]	No	Lung cancer rates in pottery workers were compared with local mortality rates.

Table 15 (Continued). IARC^{*}-reviewed epidemiologic studies having the least confounded investigations of an association between occupational exposure to crystalline silica and lung cancer

Reference and country	Study design, cohort, and followup	Subgroup	Number of lung cancer deaths or cases	Risk measure [†]	CI [‡]	Smoking information available and analyzed	Comments
Costello and Graham [1988], United States	Mortality study of 5,414 white male workers in Vermont granite sheds and quarries employed between 1950 and 1982 with at least one radiologic examination in the worker surveillance program.	Quarry workers Shed workers: Started before 1940, latency period ≥40 yr, tenure ≥30 yr Started after 1940, latency period ≥25 yr, tenure ≥10 yr	20 98 47 17	0.82 1.27 1.81 1.73	Not reported Not reported ^{§§} 1.33–2.41 ^{***} 1.01–2.77	No —	Dust exposure data were not included, limiting conclusions about exposure-response. Cohort overlaps with cohort of Davis et al. [1983]. CIs reported by IARC [1997].
Costello et al. [1995], United States	Mortality study of 3,246 male workers employed ≥1 yr between 1940 and 1980 at 20 U.S. crushed stone (i.e., granite, limestone, traprock, or sandstone) operations.	Whites Nonwhites Workers in granite facilities with ≥20-yr latency period and ≥10-yr tenure	40 11 7	1.2 1.9 3.5	0.9–1.6 0.9–3.3 1.4–7.3	No —	—
		Workers in limestone facilities Workers in traprock facilities	23 3	1.5 0.6	1.0–2.3 0.1–1.8		

See footnotes at end of table.

Table 15 (Continued). IARC^{*}-reviewed epidemiologic studies having the least confounded investigations of an association between occupational exposure to crystalline silica and lung cancer

Reference and country	Study design, cohort, and followup	Subgroup	Number of lung cancer deaths or cases	Risk measure [†]	CI [‡]	Smoking information available and analyzed	Comments
Dong et al. [1995], China	Mortality study of lung cancer in 6,266 male silicotic and nonsilicotic refractory brick workers employed before 1962 and followed for mortality from 1963 to 1985. 11,470 nonsilicotic male steel workers used as controls.	Silicotics Silicotics in Chinese radiological category: I II III Nonsilicotics	35 21 10 4 30	2.1 ^{†††} 2.0 2.3 2.6 1.1	Not reported*** Not reported*** Not reported ^{§§} Not reported ^{§§} Not reported***	Yes	Twofold excess lung cancer mortality occurred in both smokers and nonsmokers. Exposure-response trends were found for years since first employment and lung cancer mortality, and for severity of silicosis and lung cancer mortality.
Guénel et al. [1989], Denmark	Cohort study of 2,175 Danish stone workers who met the following criteria: • were alive on Jan. 1, 1943, or were born later, and • were aged <65 when first identified in one of 6 data sources. The cohort included 2,071 cancer cases identified in the Danish cancer registry between 1943 and 1984.	Lung cancer cases	44	2.00 ^{††††}	1.49–2.69	Yes	Adjusted for regional differences in smoking. Lung cancer mortality highest among Copenhagen sandstone cutters hired before 1940 prior to ventilation improvements.

See footnotes at end of table.

Table 15 (Continued). IARC^{*}-reviewed epidemiologic studies having the least confounded investigations of an association between occupational exposure to crystalline silica and lung cancer

Reference and country	Study design, cohort, and followup	Subgroup	Number of lung cancer deaths or cases	Risk measure*	CI†	Comments
McDonald et al. [1995], United Kingdom	Preliminary report of proportionate mortality study of 7,020 pottery workers born between 1916 and 1945 with mortality followup to June 30, 1992. Preliminary nested case-control study of 75 lung cancer cases and 75 controls.	Lung cancer deaths in pottery workers not exposed to asbestos	112	1.22 ^{§§}	1.04–1.43 ^{‡‡}	No Preliminary results (final results in Cherry et al. [1995]).
		Smokers and nonsmokers with ≥ 10 yr of silica exposure	75	1.4 ^{††}	0.7–2.7 ^{‡‡}	Lung cancer rates in pottery workers were compared with local mortality rates.
		Smokers with ≥ 10 yr of silica exposure	47	2.8 ^{††}	1.1–7.5 ^{‡‡}	Yes ORs were adjusted for age and smoking. Test for exposure-response trend was not statistically significant ($P>0.05$) for cumulative exposure to dust or respirable silica. High OR (7.4; CI and number of deaths not reported) for lung cancer in workers who smoked >20 cigarettes per day.

Respirable Crystalline Silica

CIs reported in IARC monograph [1997].

See footnotes at end of table.

(Continued)

Table 15 (Continued). IARC*-reviewed epidemiologic studies having the least confounded investigations of an association between occupational exposure to crystalline silica and lung cancer

Reference and country	Study design, cohort, and followup	Subgroup	Number of lung cancer deaths or cases	Risk measure [†]	CI [‡]	Smoking information available and analyzed	Comments
Merlo et al. [1991], Italy	1,022 male refractory brick workers employed at least 6 months between 1954 and 1977. Retrospective cohort study of mortality through 1986.	All brick workers Brick workers: ≤ 19 yr since 1st exposure and employed ≤ 19 yr > 19 yr since 1st exposure and employed ≤ 19 yr > 19 yr since 1st exposure and employed > 19 yr	28 7 8 13	1.51 1.05 1.75 2.01	1.00–2.18 0.42–2.16 0.75–3.46 1.07–3.44	Yes	Smoking habits of cohort comparable with the national population (includes the men in Puntoni et al. [1988]).

See footnotes at end of table.

Table 15 (Continued). IARC^{*}-reviewed epidemiologic studies having the least confounded investigations of an association between occupational exposure to crystalline silica and lung cancer

Reference and country	Study design, cohort, and followup	Subgroup	Number of lung cancer deaths or cases	Risk measure [†]	CI [‡]	Smoking information available and analyzed	Comments
Partanen et al. [1994], Finland	Cohort study of 811 male silicotics, compensated and not compensated, who were diagnosed between 1936 and 1977 in Finland. Cancer incidence for 1953–1991 was obtained from the Finnish Cancer Registry.	Length of followup from date of silicosis diagnosis: ≤2 yr 2–9 yr ≥10 yr	1 32 168	0.4 ^{***} 2.7 3.3	0.01–2.3 1.9–3.9 2.5–4.1	Yes	Update of Kurppa et al. [1986].
		Histology of lung cancers: Adenocarcinoma Squamous-cell Small-cell Other/unknown	5 34 9 53	2.0 3.2 2.1 3.0	0.6–4.6 2.3–4.5 0.9–3.9 2.2–3.9		No evidence of confounding by tobacco smoking.
		Industry: Mining/quarrying (excluding granite) Granite Glass/ceramic Grinding/sharpening Casting/founding Construction Excavation/foundation	38	3.7	2.6–5.0		
			13	2.9	1.6–5.0		
			10	3.3	1.6–6.1		
			3	3.0	.6–8.7		
			22	1.8	1.1–2.6		
			2	10	1.3–37		
			9	5.8	2.7–11.1		

See footnotes at end of table.

Table 15 (Continued). IARC^{*}-reviewed epidemiologic studies having the least confounded investigations of an association between occupational exposure to crystalline silica and lung cancer

Reference and country	Study design, cohort, and followup	Subgroup	Number of lung cancer deaths or cases	Risk measure [†]	CI [‡]	Smoking information available and analyzed	Comments
Steenland and Brown [1995b], United States	Cohort study of 3,328 white male gold miners employed underground ≥ 1 yr between 1940 and 1965 and followed for mortality from 1977 to 1990. Mortality rates of U.S. males used for comparison.	—	115	1.13	0.94–1.36	Yes	High historical exposures. No exposure-response trend by cumulative dust exposure.

Source: IARC [1997].

*Abbreviations: CI=confidence interval; IARC=International Agency for Research on Cancer; PMR=proportional mortality ratio; OR=odds ratio; SIR=standardized incidence ratio; SMR=standardized mortality ratio; SRR=standardized rate ratio

[†]SMR unless otherwise noted.

[‡]95% CI unless otherwise noted.

[§]Workers who had no known exposure to other occupational carcinogens such as asbestos manufacturing, insulation work, olivine mining, talc, and foundry work.

^{**}Nonsilicotics are subjects with normal radiographs.

^{††}OR.

^{‡‡}90% CI.

^{§§} $P < 0.05$.

^{***} $P < 0.01$.

^{†††}Values in this study are SRRs.

^{‡‡‡}Values in this study are SIRs.

^{§§§}PMR.

of diatomaceous earth workers [Checkoway et al. 1993, 1996] by including deaths after 1987 and through 1994, and by analyzing lung cancer risk among workers with radiographic silicosis. Lung cancer mortality risk was highest in the highest category of cumulative exposure to respirable crystalline silica (rate ratio with no exposure lag period=2.11; 95% CI=1.07–4.1; rate ratio for 15-year exposure lag period=1.05; 95% CI=0.99–1.11). The rate ratios were adjusted for the effects of age, calendar year, duration of followup, and ethnicity. Among workers with radiological silicosis (ILO category $\geq 1/0$ or large opacity; n=81), the lung cancer SMR was 1.57 (95% CI=0.43–4.03) [Checkoway et al. 1999]. For workers without silicosis (ILO category <1/0), the SMR was 1.19 (95% CI=0.87–1.57). The SMRs were adjusted for age and calendar year and were based on the expected number of deaths for white U.S. males. For the nonsilicotic workers, a statistically significant, positive dose-response relationship ($P=0.02$) was observed between SMRs for lung cancer and category of cumulative respirable silica exposure. The SMRs ranged from 1.05 in the lowest exposure category (<0.5 mg/m³ · year, 13 deaths, 95% CI=0.56–1.79) to 2.40 in the highest exposure category (≥ 5.0 mg/m³ · year; 12 deaths, 95% CI=1.24–4.20). For the 81 workers with radiographic silicosis, an SMR >1.0 was observed only in the highest exposure category (i.e., ≥ 5.0 mg/m³ · year) (4 deaths observed; SMR=2.94; 95% CI=0.80–7.53). These results suggest that silicosis may not be a necessary condition for silica-related lung cancer. However, radiographic surveillance of this cohort did not extend beyond the dates of employment termination, and autopsies were not routinely conducted [Checkoway et al. 1999].

Cherry et al. [1998] finalized the preliminary results of a nested case-control study of 52 lung cancer deaths in 5,115 pottery workers (see Burgess et al. [1997], Cherry et al. [1997], and McDonald et al. [1997] in Table 15). After

adjustment for smoking and inclusion of a 20-, 10-, or 0-year lag period, mean respirable silica concentration (i.e., estimated daily 8-hr TWA airborne concentrations in $\mu\text{g}/\text{m}^3$) was associated with lung cancer ($P<0.008$ for each lag period):

<i>Lag</i>	<i>OR</i>	<i>95% CI</i>
20 yr	1.60	1.11–2.31
10 yr	1.66	1.14–2.41
0 yr	1.67	1.13–2.47

However, exposure duration and cumulative silica dust exposure were not significantly associated with lung cancer mortality, regardless of lag time [Cherry et al. 1998]. The presence of small, parenchymal radiographic opacities (ILO category $\geq 1/0$) was not related to lung cancer mortality before adjustment for smoking ($P=0.78$) or after adjustment for smoking and mean silica concentration ($P=0.68$). The authors concluded “that crystalline silica may well be a human carcinogen” [Cherry et al. 1998].

Other studies published since the IARC review also investigated exposure-response associations for lung cancer and exposure to crystalline silica. Rafnsson and Gunnarsdóttir [1997] reported that the incidence of lung cancer cases among 1,346 diatomaceous earth workers in Iceland was not statistically significant for workers who had 9 years before start of followup and who were employed ≥ 5 years (standardized incidence ratio [SIR] based on 3 cases observed=2.70; 95% CI=0.56–7.90) or employed ≤ 5 years (SIR based on 2 cases observed=1.19; 95% CI=0.14–4.30).

de Klerk and Musk [1998] conducted a cohort study of 2,297 surface and underground gold miners in western Australia who participated in surveys of respiratory symptoms, smoking habits, and lung function in 1961, 1974, and 1975. Eighty-nine percent of the cohort was

traced to the end of 1993 for trachea, bronchus, and lung cancer mortality and incidence of compensated silicosis (i.e., compensation awarded by the Pneumoconiosis Medical Board). A nested case-control analysis of the 138 lung cancer deaths found that lung cancer mortality was related to log total cumulative silica dust exposure after adjustment for smoking (cigarette, pipe, or cigar) and for the presence of bronchitis at survey (relative rate=1.31; 95% CI=1.01–1.70). However, the effect of cumulative silica dust exposure on lung cancer mortality was not significant after adjustment for smoking, bronchitis, and compensation for silicosis (relative rate=1.20; 95% CI=0.92–1.56). Other silica exposure variables (i.e., duration of underground or surface employment and intensity of underground or surface exposure) were not significantly related to lung cancer mortality ($P>0.15$) after adjustment for smoking and bronchitis. Cigarette smoking (relative rate=32.5; 95% CI=4.4–241.2 for ≥ 25 cigarettes smoked per day), incidence of a compensation award for silicosis after lung cancer diagnosis (relative rate=1.59; 95% CI=1.10–2.28), and presence of bronchitis at survey (relative rate=1.60; 95% CI=1.09–2.33) were significantly related to lung cancer mortality [de Klerk and Musk 1998]. The results of this study do not support a relationship between lung cancer and silica exposure in the absence of silicosis (i.e., a compensation award for silicosis after lung cancer diagnosis). However, controlling for silicosis compensation and bronchitis may have masked a silica effect because both are markers of silica exposure.

Hnizdo et al. [1997] conducted a nested case-control study of lung cancer deaths in a cohort of 2,260 white South African underground gold miners. (A lung cancer mortality cohort study had been conducted earlier [Hnizdo and Sluis-Cremer 1991]). The mineral content of the rock in the gold mines was mostly quartz (70%–90%), silicates (10%–30%),

pyrite (1%–4%), and heavy minerals with grains of gold and uranium-bearing minerals (2%–4%). Seventy-eight miners who died from lung cancer (69 of the 78 had a necropsy) during 1970–1986 were matched by year of birth with 386 control subjects from the same cohort [Hnizdo et al. 1997]. Conditional logistic regression models were used to analyze the relationship of lung cancer mortality with cigarette smoking (pack-years), cumulative “dust” exposure ($\text{mg}/\text{m}^3 \cdot \text{year}$), years of underground mining, incidence of radiographic silicosis (ILO category $\geq 1/1$ diagnosed up to 3 years before death of a matched case), and uranium production or uranium grade of the ore in the gold mine. Radon progeny measurements in the gold mines were not available.

Lung cancer mortality was associated with cigarette smoking, cumulative dust exposure (lag time was 20 years from death), duration of underground mining (lag time was 20 years from death), and silicosis. The best-fitting model predicted relative risks of 2.45 (95% CI=1.2–5.2) for silicosis and the following relative risks for various pack-years of smoking:

<i>Pack-years</i>	<i>95% CI</i>	<i>Relative risk</i>
<6.5	—	1
6.5–20	0.7–16.8	3.5
21–30	1.3–25.8	5.7
>30	3.1–56.2	13.2

The authors stated that variables representing uranium mining were not significantly related to lung cancer mortality (modeling results for these variables were not presented) [Hnizdo et al. 1997]. The authors proposed three explanations for their results:

- Miners with high dust exposure who develop silicosis have increased lung cancer risk.

- High silica dust exposure concentrations are important in the pathogenesis of lung cancer, and silicosis is coincidental.
- High silica dust exposure concentrations are a surrogate measure of exposure to radon progeny [Hnizdo et al. 1997].

3.4.2.2 Lung Cancer Meta-Analyses

Meta-analysis and other systematic literature review methods are useful tools for summarizing exposure risk estimates from a large amount of information [Mulrow 1994]. Meta-analyses or summary reviews of epidemiologic studies of silicotics with lung cancer have been conducted by investigators in the United States [Steenland and Stayner 1997; Smith et al. 1995] and Japan [Tsuda et al. 1997]. IARC is performing a pooled analysis of epidemiologic data from several cohorts to investigate lung cancer risks in nonsilicotic workers.

Steenland and Stayner [1997] and IARC [1997] found that the majority of studies of silicotics reported statistically significant excess lung cancer risks across different countries, industries, and time periods while controlling for the effects of cigarette smoking [Steenland and Stayner 1997; IARC 1997]. Exposure-response gradients were also observed. The summary relative risk was 2.3 (95% CI=2.2–2.6) for 19 cohort and case-control studies of silicotics—excluding studies of miners and foundry workers because of potential exposure to other carcinogens, and omitting autopsy studies and proportionate mortality studies because of possible selection biases [Steenland and Stayner 1997]. Fifteen of the 19 studies directly or indirectly controlled for the effects of smoking. The summary relative risk of 16 cohort* and case-control studies

of silica-exposed workers was 1.3 (95% CI= 1.2–1.4)—a moderate and statistically significant relative risk estimate [Steenland and Stayner 1997]. Eight of the 16 studies controlled for the effects of smoking, either directly or indirectly.

Another meta-analysis of 23 lung cancer studies of silicotics (including 14 of the studies analyzed by Steenland and Stayner [1997]) reported a pooled risk estimate of 2.2 (95% CI= 2.1–2.4) [Smith et al. 1995]. The statistically significant pooled risk estimates from both meta-analyses strongly support an association between silicosis and lung cancer. The increased risk of lung cancer for silicotics is also supported by the following [IARC 1997]:

1. The magnitude of the risk estimates (i.e., most studies reported risks greater than 2.0 for silicotics after adjusting for the effects of cigarette smoking—compared with exposed nonsilicotics or the general population)
2. The observation of exposure-response gradients with various indicators of exposure
3. Consistent findings of excess risk in different countries, industries, and time periods
4. Two studies that provided reasonable evidence for an unconfounded association (i.e., Amandus et al. [1991, 1992, 1995] and Partanen et al. [1994], an update of Kurppa et al. [1986])

Tsuda et al. [1997] conducted a lung cancer meta-analysis of pneumoconiosis or silicosis studies (excluding asbestosis). Lung cancer risk estimates were pooled from 32 mortality studies published from 1980 to 1994. The estimated rate ratios were similar to those reported by Steenland and Stayner [1997] and Smith et al. [1995]:

*Cohort size ranged from 969 to 6,266 workers.

	<i>Rate ratio</i>	<i>95% CI</i>
All studies (32 [†])	2.74	2.60–2.90
Cohort studies only		
(25 of 32)	2.77	2.61–2.94
Case-control studies		
(5 of 32).	2.84	2.25–3.59

3.4.3 Other Cancers

Mortality studies of workers have reported statistically significant excesses of deaths from stomach or gastric cancer in iron ore miners [St. Clair Renard 1984; Lawler et al. 1985; Mur et al. 1987], Canadian gold miners [Muller et al. 1983; Shannon et al. 1987; Miller et al. 1987; Kusiak et al. 1993b], lead and zinc miners [Belli et al. 1989], brick production workers [Katsnelson and Mokronosova 1979], foundry and other metal workers [Neuberger and Kundi 1990], jewelry workers [Hayes et al. 1993; Dubrow and Gute 1987; Sparks and Wegman 1980], farmers (reviewed by Blair and Zahm [1991]), and farm workers [Stubbs et al. 1984] (reviewed by Zahm and Blair [1993]). A recent case-control study of 250 male hospital patients in Canada found a statistically significant excess of pathologically confirmed stomach cancer among the 25 patients who reported a history of “substantial” occupational exposure to crystalline silica compared with 2,822 controls ($OR=1.7$; 95% CI=1.1–2.7 after adjusting for the effects of age, birthplace, education, and cigarette smoking) [Parent et al. 1998]. However, in a review of epidemiologic studies of gastric cancer and dusty occupations, Cocco et al. [1996] noted that because most studies did not adjust for the effects of confounding factors or assess a dose-response relationship, evidence was insufficient to conclude that silica is a gastric carcinogen.

For workers who may have been exposed to crystalline silica, there have been infrequent reports of statistically significant excesses of deaths or cases of other cancers such as nasopharyngeal or pharyngeal cancer [Chen et al. 1992; Carta et al. 1991], salivary gland cancer [Zheng et al. 1996], liver cancer [Chen et al. 1992; Hua et al. 1992], bone cancer [Forastiere et al. 1989; Steenland and Beaumont 1986], pancreatic cancer [Kauppinen et al. 1995], skin cancer [Partanen et al. 1994; Rafnsson and Gunnarsdóttir 1997], esophageal cancer [Pan et al. 1999; Xu et al. 1996; Belli et al. 1989], cancers of the digestive system [Decoufle and Wood 1979], intestinal or peritoneal cancer [Amandus et al. 1991; Goldsmith et al. 1995; Costello et al. 1995], lymphopoietic or hematopoietic cancers [Redmond et al. 1981; Silverstein et al. 1986; Steenland and Brown 1995b], brain cancer [Rafnsson and Gunnarsdóttir 1997], and bladder cancer [Bravo et al. 1987]. Again, an association has not been established between these cancers and exposure to crystalline silica.

3.5 Other Nonmalignant Respiratory Diseases and Related Conditions

3.5.1 COPD

3.5.1.1 Definition

COPD describes chronic airflow limitation that is usually irreversible [ATS 1987; Becklake 1992; Snider 1989]. COPD includes four interrelated disease processes: chronic bronchitis, emphysema, asthma [Barnhart 1994; Snider 1989], and peripheral airways disease [ATS 1987]. Cigarette smoking is a major cause of COPD, but community air pollution and occupational exposure to dust, particularly among smokers, also contribute to COPD [Becklake 1992].

[†]Two of the studies are proportionate mortality studies for which rate ratios were not reported.

3.5.1.2 Epidemiologic Studies

Although thousands of studies have been published about occupational exposure to nonorganic dusts and COPD, only 13 studies of 4 cohorts of silica-exposed workers met rigorous methodologic criteria for a review conducted by Oxman et al. [1993]. Three of the cohorts were coal miners and one was South African gold miners. According to Oxman et al. [1993], the studies provided evidence that exposure to gold mine dust is an important cause of COPD, particularly in smokers, and that the risk of COPD appeared to be greater for gold miners than for coal miners.

3.5.2 Asthma

Crystalline silica has not been identified as an occupational asthma-inducing agent [Chan-Yeung 1994], and no published epidemiologic studies have specifically investigated whether asthma is related to crystalline silica dust exposure.

3.5.3 Chronic Bronchitis

3.5.3.1 Definition

Chronic bronchitis is clinically defined as the occurrence of chronic or recurrent bronchial hypersecretion (i.e., a productive cough) on most days of the week for at least 3 months of 2 sequential years [ATS 1987, 1995; Barnhart 1994]. The excess mucus secretion should not be related to a disease such as TB [ATS 1987, 1995]. Chronic bronchitis has been associated with both airflow obstruction and abnormalities in gas exchange [Barnhart 1994]. Although the terms “industrial bronchitis” and “occupational bronchitis” traditionally refer to chronic bronchitis that is associated with occupational exposure, bronchitic symptoms may also occur after occupational exposures that are acute or that last less than 2 years. An association between reduced ventilatory function and bronchitic symptoms has been reported in studies of

workers exposed to coal dust, asbestos, or dust that contained crystalline silica [Barnhart 1994]. However, cigarette smoking is also associated with chronic bronchitis and must be considered when investigating the relationship between occupational exposures and bronchitic symptoms [Barnhart 1994; ATS 1997].

3.5.3.2 Epidemiologic Studies

Statistically significant ($P < 0.05$) relationships independent of smoking were found between exposure[‡] to gold mine dust and chronic bronchitis or chronic sputum production in cross-sectional studies of gold miners in South Africa [Wiles and Faure 1977; Cowie and Mabena 1991] and Australia [Holman et al. 1987]. However, no statistically significant relationships independent of smoking were found between exposure and chronic bronchitis or bronchitic symptoms in cross-sectional studies of molybdenum miners [Kreiss et al. 1989b], uranium miners [Samet et al. 1984], taconite miners [Clark et al. 1980], Indian agate grinders and chippers [Rastogi et al. 1991], and a population-based study of South African gold miners [Sluis-Cremer et al. 1967] (Table 16).

Wiles and Hnizdo [1991] studied the relationship between mortality, airflow obstruction, and mucus hypersecretion in 2,065 South African gold miners. They found that after standardization for airways obstruction, mucus hypersecretion was not related to mortality from COPD (54 deaths). However, mucus hypersecretion remained significantly related to mortality from ischemic heart disease and all causes of death, even after adjustment for years of cigarette smoking and particle-years of exposure to gold mine dust [Wiles and Hnizdo 1991].

[‡]Cumulative exposure, duration of exposure, or intensity of exposure.

Table 16. Epidemiologic studies of bronchitis in workers exposed to silica dust

Reference and country	Study design, cohort, and followup	Subgroup	Bronchitis cases in subgroup*	Risk measure (OR [†])	95% CI	Adjusted for smoking	Comments
Clark et al. [1980], United States	Cross-sectional study of bronchitic symptoms in 249 white male taconite miners; mean age was 49 with ≥20 yr of exposure to taconite dust. Control group of 86 men with no history of exposure to taconite mine dust.	80 dust-exposed smokers with cough all day	24%	—‡	—	Yes	Note that subgroups represent bronchitic symptoms—not cases. 33 controls were employees of a school; however, occupations of the other controls were not reported. Occupational dust exposures to the control group may have contributed to the similar or higher prevalences of bronchitic symptoms in that group.
		52 dust-exposed nonsmokers with cough all day	1%	—	—		
		24 nondust-exposed nonsmokers with cough all day	1%	—	—		
		32 nondust-exposed smokers with cough all day	16%	—	—		
		80 dust-exposed smokers with phlegm all day	18%	—	—		
		24 nondust-exposed nonsmokers with phlegm all day	1%	—	—		
		32 nondust-exposed smokers with phlegm all day	37%	—	—		

See footnotes at end of table.

Table 16 (Continued). Epidemiologic studies of bronchitis in workers exposed to silica dust

Reference and country	Study design, cohort, and followup	Subgroup	Bronchitis cases in subgroup*	Risk measure (OR [†])	95% CI	Adjusted for smoking	Comments
Cowie and Mabena [1991], South Africa	Cross-sectional study of 1,197 black, male underground gold miners aged 28–76 with 25.1 yr since first exposure (mean). 857 miners had chronic silicosis.	Miners with chronic sputum production and “high” dust exposure Miners with 24 pack-yr of smoking exposure and chronic sputum production	— —	1.8 [§] 3.7	1.19–2.69 2.62–5.23 ^{**}	Yes	62% of miners who smoked and 45% of miners who never smoked had “chronic bronchitic symptom complex.” “High” and “low” dust exposure categories were based on qualitative assessments of underground mine dust exposure and occupation. Authors stated that bronchitic symptoms may also have been related to underground mining exposures other than respirable quartz dust.

See footnotes at end of table.

Table 16 (Continued). Epidemiologic studies of bronchitis in workers exposed to silica dust

Reference and country	Study design, cohort, and followup	Subgroup	Bronchitis cases in subgroup*	Risk measure (OR [†])	95% CI	Adjusted for smoking	Comments
Holman et al. [1987], Australia	Cross-sectional study of 1,363 male, current gold miners (51% were underground miners) aged 20 to >60. 53% of the cohort worked underground 1–19 yr.	Total cohort Miners with chronic bronchitis: 1–9 yr of underground gold mining 10–19 yr of underground gold mining ≥20 yr of underground gold mining	14% ^{‡†} — — —	— 1.8 2.5 5.1	— 1.0–3.3 1.2–5.2 2.4–10.9	Yes	ORs were based on comparison with nonminers and were adjusted for effects of smoking and age.
Kreiss et al. [1989b], United States	Community-based cross-sectional study of 389 male residents of Leadville, CO. 281 (72.2%) of the sample had worked at the local molybdenum mine. Mean yr of exposure: 9.3. Mean age of cohort: 44.	Underground miners with >10 yr of employment: With chronic cough With chronic phlegm	— — —	0.84 0.93	0.37–1.90 0.42–2.06	Yes	ORs were based on comparison with residents having no history of occupational dust exposure. Nearly half (49%) of personal samples for quartz exposures among the miners exceeded the NIOSH REL of 0.05 mg/m ³ (total number of samples was not reported).

See footnotes at end of table.

(Continued)

Table 16 (Continued). Epidemiologic studies of bronchitis in workers exposed to silica dust

Reference and country	Study design, cohort, and followup	Subgroup	Bronchitis cases in subgroup*	Risk measure (OR [†])	95% CI	Adjusted for smoking	Comments
Ng et al. [1992b], Singapore	Cross-sectional study of 85 granite quarry workers with "high" dust exposure: All (85) Nonsmokers (34) Ex-smokers (5) Current smokers (46)	Quarry workers with "high" dust exposure: All (85) Nonsmokers (34) Ex-smokers (5) Current smokers (46)	9 2 — 7	— ^{‡‡} — ^{§§} — — ^{§§}	— ^{‡‡} — ^{§§} — — ^{§§}	Yes	No quantitative exposure concentrations for dust or silica were reported: granite quarry rock drillers and rock crushers were assumed to have "high" silica exposure; and administrative workers, truck drivers, vehicle maintenance workers, and loader operators were assumed to have "low" silica exposure.

Results were adjusted for effects of age.

See footnotes at end of table.

Table 16 (Continued). Epidemiologic studies of bronchitis in workers exposed to silica dust

Reference and country	Study design, cohort, and follow up	Subgroup	Bronchitis cases in subgroup*	Risk measure (OR [†])	95% CI	Adjusted for smoking	Comments
Rastogi et al. [1991], India	Cross-sectional study of 240 male and 102 female agate grinders and chippers, and 116 male and 33 female controls with nondusty occupations. The mean duration of exposure was 10 yr for males and 8.9 yr for females.	Chronic bronchitis: Male: Agate workers Controls Female: Agate workers Controls	3.75/100 4.58/100 0 9.1/100	— — — —	— — — —	Yes	Association between dust exposure and chronic bronchitis may not have been detected because the control group included workers who may have occupational exposure to respirable silica dust (e.g., rickshaw-pullers and sweepers). High prevalence of tuberculosis in agate workers and controls may have masked an association for bronchitis.
Samet et al. [1984], United States	Cross-sectional study of 192 male, current underground uranium miners aged <40, 40–59, and ≥ 60. 145 miners (76%) mined ≥ 10 yr underground.	Miners with chronic cough: 10–19 yr of mining ≥ 20 yr of mining Miners with chronic phlegm: 10–19 yr of mining ≥ 20 yr of mining	14.1/100*** 22.7/100*** 31.9/100*** 36.6/100***	— — — —	— — — —	Yes	Chronic cough and chronic phlegm were not associated with duration of silica exposure in multiple logistic regression analysis (results were not reported).

See footnotes at end of table.

(Continued)

Table 16 (Continued). Epidemiologic studies of bronchitis in workers exposed to silica dust

Reference and country	Study design, cohort, and followup	Subgroup	Bronchitis cases in subgroup*	Risk measure (OR [†])	95% CI	Adjusted for smoking	Comments
Sluis-Cremer et al. [1967], South Africa	Community-based, cross-sectional study of chronic bronchitis in 827 male residents who were aged >35 and who lived in Carletonville, a South African town with four gold mines.	Residents w/chronic bronchitis: Dust-exposed: Smokers Nonsmokers Nondust-exposed: Smokers Nonsmokers and ex-smokers	199/394 (51%) 22/168 (13%) 45/161 (28%) 7/104 (7%)	— — — — —	— — — — —	Yes	“Dust-exposed” was defined as self-reported occupational exposure in a “scheduled dusty area” of a mine. A significant difference existed between the prevalence of chronic bronchitis in dust-exposed smokers and nondust-exposed smokers ($P<0.01$).
Wiles and Faure [1977], South Africa	Cross-sectional study of chronic bronchitis in 2,209 underground gold miners (race not reported) aged 45–54 with ≥10 yr of employment. 653 were ex-miners for ≥1 yr.	138 miners in highest cumulative dust exposure group: Nonsmokers Ex-smokers Smokers	2/14 (14%) 4/31 (13%) 47/93 (51%)	— — —	— — —	Yes	Prevalence of chronic bronchitis increased with increasing mean dust concentration ($P<0.001$) and with cumulative dust exposure in nonsmokers ($P<0.05$), ex-smokers ($P<0.05$), and smokers ($P<0.001$).

^{*}Number of cases unless otherwise indicated.[†]Abbreviations: CI=confidence interval; NIOSH=National Institute for Occupational Safety and Health; OR=odds ratio; REL=recommended exposure limit.[‡]Dash indicates *not reported*.[§]Compared with miners having “low” dust exposure.^{**}Compared with miners having 0 pack-yr.^{††}Estimated prevalence.^{‡‡}Risk measure was not reported, but $P<0.01$ compared with controls.^{§§}Risk measure was not reported, but $P>0.05$ compared with controls.^{***}Standardized to the overall distribution of cigarette smoking.

A mortality study of workers in “dusty trades” reported a statistically significant number of deaths from bronchitis when compared with mortality rates for other white males in the United States ($P<0.05$; 6 deaths observed; 0.8 deaths expected) [Amandus et al. 1991].

The discrepancies among the cross-sectional studies of bronchitis in quartz-exposed populations may be attributable to the presence or absence of concurrent exposures among the cohorts that have been studied [Kreiss et al. 1989b]. Particle size is another factor that may have affected the results. The dust in one work environment may have had a higher proportion of particles that were not of respirable size[§] compared with dust in another work environment. Larger-sized dust particles may be responsible for large-airways diseases such as chronic bronchitis, whereas respirable dust particles are responsible for lung parenchymal diseases such as silicosis [Morgan 1978]. In addition to physical size, the shape and density of inorganic dust particles also influence where they are deposited in the airways and whether they can be cleared from the airways [Becklake 1985].

3.5.4 Abnormalities in Pulmonary Function Tests

3.5.4.1 Definition

Pulmonary function tests measure lung volumes (e.g., vital capacity [VC]), air flow (e.g., expiratory volume in 1 second [FEV_1]), blood gas exchange, and other aspects of lung function [Rosenstock 1994]. Spirometric pulmonary function tests routinely performed are forced vital capacity (FVC), FEV_1 , and VC [Parkes 1982]. Lung function tests alone cannot diagnose any particular disease [Parkes 1982]; however, they are an important part of

the clinical evaluation of workers with occupational lung diseases. Nonoccupational factors (e.g., the subject’s age, height, racial group, and smoking habit) as well as the quality and interpretation of the spirometric testing can influence pulmonary function test results [Parkes 1982; Rosenstock 1994; Crapo 1994]. In general, an FEV_1 loss of about 20 to 30 ml/year in nonsmokers or >60 ml/year in smokers [Crapo 1994] may suggest a decline greater than expected. Wagner [1994] suggests further clinical evaluation of workers with a 15% decrease from the baseline percentage of predicted value for FEV_1 or FVC (e.g., from 105% to 90% of the predicted FEV_1).

Loss of FEV_1 has been associated with an increased risk of death from various diseases, including COPD [Crapo 1994; Tockman and Comstock 1989; Anthonisen et al. 1986; Foxman et al. 1986]. Although pulmonary function tests can define and measure respiratory impairment, they are not a diagnostic tool for silicosis or a measure of silica exposure [Wagner 1997], because no single pattern of pulmonary function abnormality is associated with silica exposure or silicosis [Wagner 1997; Weill et al. 1994; ATS 1997].

3.5.4.2 Epidemiologic Studies—Quantitative Estimates of Dust-Related Loss of Lung Function

Most epidemiologic studies of pulmonary function and occupational exposure to respirable crystalline silica are cross-sectional studies that do not provide quantitative modeling of cumulative dust exposure. They report occupationally related annual declines in ventilatory function in workers with and without silicosis (i.e., gold and other hard-rock miners, iron ore miners, coal miners, talc miners, slate workers, and kaolin workers). Details of these studies are reported elsewhere [ATS 1997; Becklake

[§]Respirable particles have aerodynamic diameters less than approximately 10 μm .

1985, 1992; Eisen et al. 1995; NIOSH 1995a; EPA 1996; Graham et al. 1994].

Thirteen studies with quantitative dust exposure data for four silica-exposed cohorts found statistically significant associations between loss of lung function (i.e., FEV₁, FVC) and cumulative respirable dust exposure in coal miners and South African gold miners [Oxman et al. 1993]. The study of gold miners [Hnizdo 1992] estimated that a 50-year-old, white South African gold miner (nonsmoker) who was exposed to gold mine dust (containing 0.09 mg/m³ of crystalline silica) at an average respirable concentration of 0.3 mg/m³ for 24 years would lose 236 ml of FEV₁ (95% CI= 134–337). This loss is equivalent to about half of the estimated loss of FEV₁ in a typical U. S. male (nonminer) who smoked one pack of cigarettes per day for 30 years (i.e., 552 ml [95% CI=461–644]) [Dockery et al. 1988; Hnizdo 1992]. The combined effects of respirable dust exposure and smoking on the loss of FEV₁ were additive [Hnizdo 1992].

Epidemiologic studies of Vermont granite workers provided quantitative predictions of FEV₁ loss based on cumulative past exposure to granite dust. As shown in Table 17, the predicted FEV₁ loss for Vermont granite workers is 3 to 4 ml per mg/m³ · year for cumulative exposure to granite dust and 2.9 ml per mg/m³ · year for cumulative exposure to quartz dust. This estimate represents a loss of about 6.5 ml of FEV₁ for a working lifetime (i.e., 45 years) of exposure to crystalline silica at the current NIOSH REL of 0.05 mg/m³. However, the findings of Theriault et al. [1974b] were based on measurements that may have been inaccurate. In 1979, Graham et al. [1981] administered pulmonary function testing to about 73% (n=712) of the workers tested in 1974 and found small annual increases in FEV₁. These researchers concluded that “technical deficiencies in the previous studies led to exaggerated and erroneous estimates of loss.”

The significance of predicted losses can be compared with the annual estimated FEV₁ decline for a nonminer who smokes one pack of cigarettes per day (10 ml/year) [Xu et al. 1992] or with the approximate annual FEV₁ decrease in men over age 25 (25 to 30 ml/year) [Burrows 1986].

A cross-sectional study of 389 male residents of a U.S. hardrock mining community also predicted FEV₁ loss [Kreiss et al. 1989b]. Multiple regression analyses found a significant difference ($P \leq 0.05$) in the mean FEV₁ for nonsmokers with dust exposure (96% of predicted FEV₁) compared with that of nonsmokers without occupational dust exposure (101% of predicted FEV₁) [Kreiss et al. 1989b].

3.5.5 Emphysema

3.5.5.1 Definition

Emphysema is the abnormal enlargement of the air spaces distal to the terminal bronchiole with destructive changes in the alveolar walls [ATS 1987]. Obvious fibrosis is not present [ATS 1987, 1995; Barnhart 1994; Becklake 1992], although small emphysematous spaces are frequently seen radiographically around the edges of large silicotic masses [Weill et al. 1994]. The diagnosis of emphysema is defined by pathologic criteria, and more recently by the presence of avascular spaces on computed tomographic (CT) scans of the lung [Barnhart 1994; Hayhurst et al. 1984]. Clinical signs include hyperinflation on chest radiographs, increased total lung capacity, reduced FEV₁, reduced diffusing capacity for carbon monoxide (DLCO) [Barnhart 1994], and weight loss [Stulbarg and Zimmerman 1996]. Emphysema is caused mainly by destruction of the lung parenchyma from excess proteolytic enzymes. One cause of excess proteolytic enzymes and the premature development of emphysema is the rare homozygous deficiency of the protein α_1 -antitrypsin [Laurell and Eriksson 1963; Stulbarg and Zimmerman 1996]. Excess

Table 17. Loss of lung function (FEV₁)^{*} associated with cumulative exposure to respirable granite dust

Reference and country	Study design, cohort, and followup	Subgroup	Loss of FEV ₁			
			Observed (estimated ml/yr)	Predicted (ml per mg/m ³ ·year)	Adjusted for smoking	Comments
Eisen et al. [1995], United States	Longitudinal study of 618 white male granite workers hired after 1940, aged 25–65; employed 14.7 yr (mean), and followed 1970–1974 for annual pulmonary function testing [Eisen et al. 1983]. Quartz content of dust was 11% [Hosey et al. 1957].	Nonsmokers Smokers Nonsilicotic nonsmokers	34–72 53–69 —	— — 4 [†]	Yes	Significant dose-response ($P<0.05$) was observed in the “dropout” group but not in the “survivor” group or the total cohort [Eisen et al. 1983]. After 1940, granite dust concentrations in Vermont granite sheds were <10 million particles per cubic foot (mppcf), or a respirable silica concentration of about 0.075 mg/m ³ [Davis et al. 1983].
Theriault et al. [1974b], United States	Cross-sectional study of 792 male, current granite shed workers aged 25–65. Quartz content of dust was 9% [Theriault 1974a].	Granite dust exposure Quartz dust exposure	1.6 ^{‡§} 1.5 ^{**}	3 [§] 2.9 [§]	Yes	Predicted loss based on results of multiple regression analysis. Exposure-response relationship found between cumulative dust exposure and cumulative quartz exposure and loss of FEV ₁ .

*Forced expiratory volume in 1 second.

[†]In dropout group (i.e., subjects lost to followup). No predicted loss in survivor group.

[‡]Per dust-year (i.e., granite shed dust exposure of 0.52 mg/m³ for 40 hr/week for 1 yr).

[§]Included silicotics.

^{**}Per quartz-year (i.e., quartz dust exposure of 0.05 mg/m³ for 40 hr/week for 1 yr).

proteolytic enzymes can also occur when there is excessive recruitment of polymorphonuclear leukocytes (e.g., from damage caused by cigarette smoke) [Stulbarg and Zimmerman 1996].

Emphysema is classified microscopically by type based on the distribution of enlarged air-spaces and destruction. The main types of emphysema include centriacinar, focal, centrilobular, panacinar, distal acinar, and irregular (scar) [Barnhart 1994; Parkes 1994]. Focal and centrilobular emphysema are the types frequently associated with environmental and occupational exposures. Focal emphysema is associated with exposure to coal dust, and centrilobular emphysema is commonly found in the upper lobes of the lungs of cigarette smokers and others exposed to chronic irritants [Barnhart 1994]. However, findings from a study of postmortem lung examinations showed that panacinar or centriacinar were the predominant types of emphysema found in the lungs of white South African gold miners [Hnizdo et al. 1991].

3.5.5.2 Epidemiologic Studies

Studies of emphysema in silica-exposed workers (excluding coal miners) show conflicting results: it is not clear whether silica exposure is associated with emphysema in all exposed workers or mainly in silica-exposed workers who smoke. In these studies, researchers have investigated cohorts of South African gold miners, usually by combining historical data about occupational exposures and smoking with postmortem examination of the lungs. (Attending physicians in South Africa who know or suspect that their deceased patient was a miner are legally required to remove the cardiorespiratory organs and send them to the Medical Bureau for Occupational Diseases if permission is granted by the next-of-kin [Goldstein and Webster 1976]).

Of the five studies presented in Table 18, one found that a significant relationship ($P<0.05$) independent of smoking and silicosis existed between gold mine dust exposure^{**} and emphysema [et al. 1987]. Two studies found no relationship between emphysema and years of mining [Chatgidakis 1963; Cowie et al. 1993]. A study of emphysema type in 1,553 miners with autopsy examinations found that centriacinar emphysema was more common in smokers, whereas panacinar emphysema was more common in nonsmokers; exposure to gold mine dust was related to both types. A miner who had worked 20 years in high-dust occupations was 3.5 times more likely (95% CI= 1.7–6.6) to have emphysema (i.e., an emphysema score $\geq 30\%$) at autopsy than a miner who did not have a dusty occupation. However, the authors stated that this result was likely to “be true of smoking miners only because there were only four nonsmokers with an emphysema score between 30% and 40%” [Hnizdo et al. 1991]. Later, a study of 242 miners who were lifelong nonsmokers found that the severity of emphysema at autopsy was not related to most recent lung function measurements or to years of gold mining, cumulative dust exposure, or parenchymal silicosis after adjustment for age at death [Hnizdo et al. 1994]. All of the studies but two [Becklake et al. 1987; Hnizdo et al. 1994] found that the presence of emphysema was significantly associated with silicosis.

3.5.6 Nonmalignant Respiratory Disease (NMRD) Mortality

Epidemiologic studies of silica-exposed workers [Checkoway et al. 1993, 1997; Chen et al. 1992; Cherry et al. 1998; Brown et al. 1986; Costello and Graham 1988; Costello et al. 1995;

^{**}The number of shifts worked in mining occupations with high dust exposure.

Table 18. Epidemiologic studies of emphysema in workers exposed to silica dust

Reference and country	Study design, cohort, and followup	Subgroup	Number of emphysema deaths or cases in subgroup	Risk measure	95% CI*	Adjusted for smoking	Comments
Becklake et al. [1987], South Africa	Unmatched case-control study of 44 autopsied white gold miners with emphysema \geq grade 2.0 (i.e., moderate or marked emphysema) and 42 controls without emphysema. Miners and controls were aged 51–70 at death (1980–1981).	Miners who smoked 20 cigarettes/day before 1960	— [†]	30.3 [‡]	7.0–141.0	Yes	The presence of emphysema at autopsy was not associated with the presence of silicosis.
Chatzidakis [1963], South Africa	Prevalence study of 800 consecutive autopsies of white gold miners conducted between January 1957 and October 1962.	Miners with silicosis and emphysema	297	44.58 [§]	— ^{**}	No	Deaths during 1980–1981 may not be typical of deaths in the total cohort of South African gold miners.

See footnotes at end of table.

Table 18 (Continued). Epidemiologic studies of emphysema in workers exposed to silica dust

Reference and country	Study design, cohort, and followup	Subgroup	Number of emphysema deaths or cases in subgroup	Risk measure	95% CI*	Adjusted for smoking	Comments
Cowie et al. [1993], South Africa	Random sample of 70 black underground gold miners selected for computed tomography lung examination from 1,197 participants in a cross-sectional study conducted in 1984–1985.	Miners by emphysema grade: Grade 0 (no evidence) Grade 1 (<25% of lung affected) Grade 2 (25%–50% of lung affected)	22 38 10	— — —	—	Yes	Presence and grade of emphysema were associated with silicosis ($P<0.002$; $P=0.006$) and smoking ($P<0.02$; $P=0.01$) but were not associated with years of underground mining. Low agreement (i.e., 37/70) between computed tomographic and radiologic assessments of silicotic nodule profusion categories.

See footnotes at end of table.

(Continued)

Table 18 (Continued). Epidemiologic studies of emphysema in workers exposed to silica dust

Reference and country	Study design, cohort, and followup	Subgroup	Number of emphysema deaths or cases in subgroup	Risk measure	95% CI*	Adjusted for smoking	Comments
Hnizdo et al. [1991], South Africa	Retrospective cohort study of the relationship of emphysema with lung function changes in 1,553 white gold miners aged ≥ 40 with autopsy examination between 1974 and 1987 and panacinar, centriacinar, or a mixed type of emphysema.	Miners who worked 20 yr in occupations with "high" dust exposure up to age 45	—	3.5‡	1.7–6.6	Yes (in some analyses)	<ul style="list-style-type: none"> • Logistic regression model showed significant association between • centriacinar emphysema and silicosis ($P < 0.001$), • emphysema and years of employment in a high-dust occupation for miners who smoked, • age and emphysema, and • average number of cigarettes smoked/day and emphysema. <p>Possible misclassification of emphysema type.</p>

See footnotes at end of table.

Table 18 (Continued). Epidemiologic studies of emphysema in workers exposed to silica dust

Reference and country	Study design, cohort, and followup	Subgroup	Number of emphysema deaths or cases in subgroup	Risk measure	95% CI*	Adjusted for smoking	Comments
Hnizdo et al. [1994], South Africa	Retrospective cohort study of relationship of emphysema with lung function in 242 white gold miners who were life-long nonsmokers, were aged ≥ 45 at death, and had an autopsy examination during 1974–1990.	Nonsmoking miners with moderate emphysema	4	—	—	Yes (all study subjects were nonsmokers)	For nonsmokers, degree of emphysema at autopsy was not associated (i.e., $P > 0.05$ in multiple regression model) with years of gold mining, cumulative dust exposure, parenchymal silicosis, or lung function impairment after adjusting for age at death.

*Abbreviations: CI=confidence interval; OR=odds ratio.

†Dash indicates *not reported*.‡OR for emphysema \geq grade 2 at autopsy.

§Chi-square value (comparing silicotic miners with emphysema to silicotic miners without emphysema).

** $P < 0.00001$.

Costello 1983; Steenland and Brown 1995b; Steenland and Beaumont 1986; Thomas and Stewart 1987; Thomas 1990] and silicotics [Goldsmith et al. 1995; Brown et al. 1997; Rosenman et al. 1995] found significant increases in mortality from NMRD, a broad category that can include silicosis and other pneumoconioses, chronic bronchitis, emphysema, asthma, and other related respiratory conditions.

The studies of U.S. gold miners [Steenland and Brown 1995b], U.S. diatomaceous earth workers [Checkoway et al. 1993, 1997], silicotic men in Sweden and Denmark [Brown et al. 1997] and parts of the United States [Rosenman et al. 1995], and U.S. pottery workers [Thomas and Stewart 1987] reported mortality ratios (SMRs or PMRs) for some categories of NMRD. However, the other studies either did not report SMRs for categories of NMRD or did not separate silicosis deaths from other categories of NMRD, thus limiting any conclusion about the association of silica exposure with death from a specific COPD based on death certificate data.

Some studies have reported exposure-response trends for NMRD and silica exposure. The study of diatomaceous earth workers found a statistically significant exposure-response trend for cumulative exposure to respirable crystalline silica and NMRD mortality after adjustment for the effects of age, calendar year, duration of followup, and ethnicity (rate ratio=5.35 in the highest exposure stratum [$\geq 5.0 \text{ mg/m}^3 \cdot \text{year}$]; 95% CI=2.23–12.80; 15-year exposure lag) [Checkoway et al. 1997]. Other studies found exposure-response trends for NMRD mortality and duration of employment [Costello et al. 1995; Thomas and Stewart 1987], years since first exposure [Thomas and Stewart 1987], or qualitative categories of silica exposure (*none, low, and high*) [Thomas and Stewart 1987].

3.6 Autoimmune and Chronic Renal Diseases

In this century, many published case reports have described various autoimmune disorders in workers or patients who were occupationally exposed to crystalline silica [Bramwell 1914; Erasmus 1957; Jones et al. 1976; Mehlhorn 1984; Mehlhorn et al. 1990a; de Bandt et al. 1991; Yanez Diaz et al. 1992; Pelmear et al. 1992; Caux et al. 1991; Cointrel et al. 1997; Yamamoto et al. 1994; Guseva 1991; Ebihara 1982; Agarwal et al. 1987; Koeger et al. 1991, 1992, 1995; Anandan et al. 1995; Sanchez-Roman et al. 1993; Aoki et al. 1988; Fukata et al. 1983, 1987; Muramatsu et al. 1989; Masuda 1981; Tokumaru et al. 1990; Perez Perez et al. 1986; Bernardini and Iannaccone 1982; Siebels et al. 1995; Suratt et al. 1977; Meyniel et al. 1981; Hatron et al. 1982; Masson et al. 1997; Ozoran et al. 1997; Haustein 1998; Cledes et al. 1982; Mehlhorn and Gerlach 1990]. The most frequently reported autoimmune diseases were scleroderma, systemic lupus erythematosus (lupus), rheumatoid arthritis, autoimmune hemolytic anemia [Muramatsu et al. 1989], and dermatomyositis or dermatopolymyositis [Robbins 1974; Koeger et al. 1991]. Case reports have also described health effects such as the following that may be related to the immunologic abnormalities in patients with silicosis: chronic renal disease [Saita and Zavaglia 1951; Bolton et al. 1981; Giles et al. 1978; Pouthier et al. 1991; Neyer et al. 1994; Dracon et al. 1990; Sherson and Jorgensen 1989; Rispal et al. 1991; Osorio et al. 1987; Bonnin et al. 1987; Arnalich et al. 1989; Wilke et al. 1996; Banks et al. 1983; Hauglustaine et al. 1980; Slavin et al. 1985], ataxic sensory neuropathy [Tokumaru et al. 1990], chronic thyroiditis [Masuda 1981], hyperthyroidism (Graves' disease) [Koeger et al. 1996], monoclonal gammopathy [Fukata et al. 1983, 1987; Aoki et al. 1988], and polyarteritis nodosa [Arnalich et al. 1989].

In addition to these case reports, 13 post-1985 epidemiologic studies reported statistically significant numbers of excess cases or deaths from known autoimmune diseases or immunologic disorders (scleroderma, systemic lupus erythematosus, rheumatoid arthritis, and sarcoidosis), chronic renal disease, and subclinical renal changes (Table 19). Epidemiologic studies found statistically significant associations between occupational exposure to crystalline silica dust and several renal diseases or effects, including end-stage renal disease morbidity [Steenland et al. 1990], morbidity from end-stage renal disease caused by glomerulonephritis [Calvert et al. 1997], chronic renal disease mortality [Steenland and Brown 1995b], Wegener's granulomatosis (systemic vasculitis often accompanied by glomerulonephritis) [Nuyts et al. 1995], and subclinical renal changes [Hotz et al. 1995; Boujema et al. 1994; Ng et al. 1992a, 1993].

The pathogenesis of glomerulonephritis and other renal effects in silica-exposed workers is not clear. Some case reports provide evidence of an immunologic injury by immune complex formation, and other reports point to a direct toxic effect of silica [Calvert et al. 1997; Calvert and Steenland 1997; Kallenberg 1995; Wilke et al. 1996; Wilke 1997]. The immunologic aspects of renal disease are reviewed in Ambrus and Sridhar [1997].

The cellular mechanism that leads from silica exposure to autoimmune diseases is not known [Otsuki et al. 1998]. One theory is that when respirable silica particles are encapsulated by macrophages, fibrogenic proteins and growth factors are generated, and ultimately the immune system is activated [Haustein and Anderegg 1998; Ziegler and Haustein 1992; Haustein et al. 1992]. Immune activation by respirable crystalline silica may be linked to scleroderma, rheumatoid arthritis, polyarthritis, mixed connective tissue disease, systemic lupus erythematosus, Sjögren's syndrome,

polymyositis, and fibrositis [Ziegler and Haustein 1992; Haustein et al. 1990; Otsuki et al. 1998]. A possible mechanism for development of scleroderma is a direct local effect of nonrespirable quartz particles that have penetrated the skin of workers [Green and Vallyathan 1996], as observed in skin samples from deceased scleroderma patients [Mehlhorn et al. 1990b].

In addition to the studies summarized in Table 19, there may be other epidemiologic data sets that have not been analyzed by methods that would detect a possible association between occupational exposure to crystalline silica and autoimmune diseases [Steenland and Goldsmith 1995]. Further clinical and immunologic studies are needed to characterize the relationship between occupational exposure to crystalline silica and autoimmune diseases.

3.7 Other Health Effects

Extrapulmonary deposits of silica have been reported. A review of the literature [Slavin et al. 1985] indicates that silica particles may be transported from the lungs and tracheobronchial lymph nodes to the spleen, liver, kidneys [Osorio et al. 1987], bone marrow, and extrathoracic lymph nodes as a result of (1) formation of silicotic lesions in pulmonary veins, (2) erosion of silicotic hilar nodules into pulmonary veins, and (3) rupture of silicotic nodules into the lymphatic system. Roperto et al. [1995] reported two cases of extrapulmonary silicosis in two water buffaloes that lived on a farm near a quartz quarry. Silicotic lesions were observed in the mesenteric lymph nodes, tonsils, and spleen. In humans with occupational exposure to silica, peritoneal silicosis has been misdiagnosed as pancreatic carcinoma [Tschoopp et al. 1992] or abdominal malignancy [Miranda et al. 1996].

Intravenous injections of silica into the tail veins of rats have resulted in large liver

Table 19. Epidemiologic studies of immunologic, autoimmune, and chronic renal disease (including subclinical renal changes) in silica-exposed workers

Reference and country	Study design, cohort, and followup	Subgroup	Number of deaths or cases in subgroup	Risk measure*	95% CI†	Comments
Boujemaa et al. [1994], Belgium	Cross-sectional case-control study of 116 silicotic, male underground miners with no history of diabetes, nephrolithiasis, or hypertension and 61 age-matched controls from the general population.	Silicotics	116	— [‡]	—	Miners were examined an average of 23 yr after cessation of exposure. Mean duration of exposure was 14.9 yr.

Urine samples were tested for albumin, retinol-binding protein, and NAG. Serum samples were tested for creatinine and β_2 -microglobulin.

Duration of exposure and severity of silicosis were not associated with the measures of renal dysfunction.

Silicotic miners had significantly higher urinary concentrations of albumin ($P=0.017$), retinol-binding protein ($P=0.0045$), and NAG ($P=0.0001$).

Results were similar to those found by Hotz et al. [1995].

Table 19 (Continued). Epidemiologic studies of immunologic, autoimmune, and chronic renal disease (including subclinical renal changes) in silica-exposed workers

Reference and country	Study design, cohort, and followup	Subgroup	Number of deaths or cases in subgroup	Risk measure*	95% CI†	Comments
Bovenzi et al. [1995], Italy	Case-control study of 527 patients admitted to all hospitals in Trento province 1976–1991 and discharged with diagnosis of musculoskeletal disorder or connective tissue disease. Each scleroderma case was matched by age and gender to two controls who were without the disease under study and were from the same database.	Patients discharged with diagnosis of systemic sclerosis (according to specific diagnostic criteria): Women Men	0‡ 16 5	5.20§	0.48–74.1	—

See footnotes at end of table.

Table 19 (Continued). Epidemiologic studies of immunologic, autoimmune, and chronic renal disease (including subclinical renal changes) in silica-exposed workers

Reference and country	Study design, cohort, and followup	Subgroup	Number of deaths or cases in subgroup	Risk measure*	95% CI†	Comments
Burns et al. [1996], United States	Population-based case-control study of 274 women with confirmed systemic sclerosis diagnosed in Michigan between 1985 and 1991 and 1,184 female controls matched by race, age, and geographic region.	Women with self-reported exposure to the following: Abrasive grinding or sandblasting	3	0.34	0.10–1.10	Adjusted for age, race, and date of birth. Systemic sclerosis was not associated with self-reported exposures to silica dust or silicone (including breast implants).
		Sculpting or pottery making	20	1.53	0.89–2.65	Same study design was applied to Ohio women with systemic sclerosis, and results were published later in a letter [Lacey et al. 1997].
		Working in a dental laboratory	3	1.52	0.44–5.26	
		Working with or near silica dust, sand, or other silica products	12	1.50	0.76–2.93	
Calvert et al. [1997], United States	Cohort morbidity study of 2,412 white, male underground gold miners employed ≥ 1 yr between 1940 and 1965 and alive on January 1, 1977.	Miners with cases of treated end-stage renal disease Nonsystemic ^{††} Systemic Unknown	11 6 4 1	1.37** 4.22** 0.80** 1.54**	0.68–2.46 1.54–9.19 0.22–2.06 0.04–8.57	First epidemiologic study to examine incidence of end-stage renal disease in an occupational cohort. Subcohort of gold miners studied by Steenland and Brown [1995b].
						Mean respirable silica dust exposure of this subcohort was 0.05 mg/m ³ .

See footnotes at end of table.

Table 19 (Continued). Epidemiologic studies of immunologic, autoimmune, and chronic renal disease (including subclinical renal changes) in silica-exposed workers

Reference and country	Study design, cohort, and followup	Subgroup	Number of deaths or cases in subgroup	Risk measure*	95% CI†	Comments
Cowie [1987], South Africa	Cohort study of incidence of scleroderma in black gold miners seen by the medical service from July 1981 to June 1986.	Miners with scleroderma that met diagnostic criteria	10	81.8 ⁺⁺	—	Same cohort studied by Bernard et al. [1994].
Hotz et al. [1995], Belgium	Cross-sectional case-control study of prevalence of subclinical renal effects in 86 quarry workers employed 11 to 20 months with no clinical, spirometric, or radiographic signs of silicosis. Controls were manual workers [Bernard et al. 1994] matched by smoking status, body mass index, and age.	—	86	—	—	Quarry workers had significantly higher urinary concentrations of albumin ($P<0.0004$), transferrin ($P<0.03$), retinol-binding protein ($P<0.001$), NAG ($P<0.001$), and silicon ($P<0.0001$). Controls may have been exposed to silica dust—occupational history of controls was not reported. Narrow range of employment duration may have limited the assessment of effects.

See footnotes at end of table.

Table 19 (Continued). Epidemiologic studies of immunologic, autoimmune, and chronic renal disease (including subclinical renal changes) in silica-exposed workers

Reference and country	Study design, cohort, and followup	Subgroup	Number of deaths or cases in subgroup	Risk measure*	95% CI†	Comments
Klockars et al. [1987], Finland	Cohort morbidity study of 1,026 granite workers hired between 1940 and 1971 with followup until the end of 1981 for (1) incidence of disability pension awards for rheumatoid arthritis during 1969–1981, (2) prevalence of rheumatoid arthritis on December 31, 1981, and (3) prevalence of subjects receiving free medication for rheumatoid arthritis at the end of 1981. Referent group was composed of Finnish males.	Granite workers: Awarded disability pensions for rheumatoid arthritis Receiving pensions for rheumatoid arthritis at end of study period	17§§ 10§§	5.08*** —	3.31–7.79 —	Mean quartz concentrations measured in the granite quarries, processing yards, and crushing plants in 1970–1972 ranged from 0.02 to 4.9 mg/m ³ . 1.6 recipients expected ($P<0.001$). —

Table 19 (Continued). Epidemiologic studies of immunologic, autoimmune, and chronic renal disease (including subclinical renal changes) in silica-exposed workers

Reference and country	Study design, cohort, and followup	Subgroup	Number of deaths or cases in subgroup	Risk measure*	95% CI†	Comments
Ng et al. [1993], Singapore	Cross-sectional study of subclinical renal effects in 67 granite quarry workers with no history of glomerulonephritis, urinary calculi, renal disease, diabetes, hypertension, or regular ingestion of analgesics. Workers' urine samples were tested for indicators of glomerular and tubular functions (i.e., albumin, AMG, BMG, and NAG).	Workers with low-dust-exposure jobs and no radiographic evidence of silicosis	31	—	—	Workers in the high-exposure group with ≥ 10 yr of employment had significantly greater ($P < 0.05$) urinary concentrations of AMG, BMG, and NAG compared with workers in the low-exposure group. Quantitative dust exposure data not available.
		Workers with high-dust-exposure jobs and < 10 yr of employment	17	—	—	
		Workers with high-dust-exposure jobs and ≥ 10 yr of employment	19	—	—	Preliminary findings were reported in Ng et al. [1992a].

See footnotes at end of table.

Table 19 (Continued). Epidemiologic studies of immunologic, autoimmune, and chronic renal disease (including subclinical renal changes) in silica-exposed workers

Reference and country	Study design, cohort and followup	Subgroup	Number of deaths or cases in subgroup	Risk measure*	95% CI†	Comments
Nuyts et al. [1995], Belgium	Case-control study of occupational exposures of 16 patients diagnosed with Wegener's granulomatosis at six Belgian renal units between June 1991 and June 1993. Each patient was matched (by age, sex, and region of residence) with two controls randomly selected from lists of voters.	Patients with Wegener's granulomatosis (renal involvement) and reported occupational exposure to silica	5	5.0	1.4–11.6	Study had small sample size and was not designed specifically to examine exposure-response relationship of Wegener's granulomatosis with occupational exposure to silica. Further study is needed.
Rafnsson et al. [1998], Iceland	Population-based case-control study of residents in a district with a diatomaceous earth processing plant. Population included 8 sarcoidosis patients who were linked to a file of all past and present workers employed at the plant after it opened in 1967. 70 controls were randomly selected from the district population.	Sarcoidosis patients with occupational exposure to diatomaceous earth and cristobalite at the community plant	6	13.2	2.0–140.9	No matching of cases with controls. Mean values of personal samples of respirable cristobalite dust taken in 1978 and 1981 ranged from 0.002 to 0.6 mg/m ³ . Stratification by number of hr worked ($\geq 1,000$ hr or $<1,000$ hr) indicated a dose-response trend. Further study of sarcoidosis and silica exposure is needed.

See footnotes at end of table.

Table 19 (Continued). Epidemiologic studies of immunologic, autoimmune, and chronic renal disease (including subclinical renal changes) in silica-exposed workers

Reference and country	Study design, cohort, and followup	Subgroup	Number of deaths or cases in subgroup	Risk measure*	95% CI†	Comments
Rosenman and Zhu [1995]	Cohort morbidity study of men and women aged ≥ 20 and discharged from Michigan hospitals 1990–1991.	Patients with silicosis and rheumatoid arthritis: Women Men	0 3	— 3.2 **	— 1.1–9.4	No patients had silicosis and scleroderma.
Sluis-Cremer et al. [1985], South Africa	Case-control study of silicosis in 79 white gold miners diagnosed with “definite” or “probable” progressive systemic sclerosis between 1955 and June 1984. Randomly selected control group of 79 miners in same patient index examined between May 1970 and April 1971; matched by age; without progressive systemic sclerosis.	— — 79	— — 1.18	— — 0.26–5.38	Although reported ORs suggested no association between silicosis and progressive systemic sclerosis, cases had higher cumulative dust exposure ($P < 0.001$).	Controlled for cumulative dust exposure.
Sluis-Cremer et al. [1986], South Africa	Case-control study of silicosis in 157 white gold miners diagnosed with “definite” or “probable” rheumatoid arthritis between 1967 and 1979. Each case was matched by age to a control subject without rheumatoid arthritis.	Miners with “definite” rheumatoid arthritis Miners with “probable” rheumatoid arthritis	91 66	3.79*** 1.94***	1.72–8.36 0.81–4.63	Although the reported ORs suggested that gold miners with probable or definite rheumatoid arthritis were more likely to have silicosis as well, the study was not designed to examine the possibility of a direct association between silica exposure and rheumatoid arthritis. The results could not be explained by cumulative dust exposure or the intensity of exposure to gold mine dust.

Table 19 (Continued). Epidemiologic studies of immunologic, autoimmune, and chronic renal disease (including subclinical renal changes) in silica-exposed workers

Reference and country	Study design, cohort, and followup	Subgroup	Number of deaths or cases in subgroup		Risk measure*	95% CI†	Comments
			*	*			
Steenland et al. [1990], United States	Population-based case-control study of occupational exposures of 325 men listed in the Michigan kidney registry and diagnosed with end-stage renal disease (excluding diabetic, congenital, and obstructive nephropathies) between 1976 and 1984. 325 controls matched by age, race, and area of residence.	Men with end-stage renal disease who reported occupational exposure to silica	87	1.67	1.02–2.74		Possible overreporting of exposure by cases.
Steenland et al. [1992], United States	Proportionate mortality study of 991 granite cutters who died after 1960 compared with causes of death in U.S. population.	Granite cutters: Arthritis deaths Chronic renal disease deaths (ICD-9 categories 582, 583, 585, 587) ***	17	2.01***	1.17–3.21		Study included all underlying and contributing causes of mortality after 1960 and other significant conditions that were documented on the death certificate.

Table 19 (Continued). Epidemiologic studies of immunologic, autoimmune, and chronic renal disease (including subclinical renal changes) in silica-exposed workers

Reference and country	Study design, cohort, and followup	Subgroup	Number of deaths or cases in subgroup	Risk measure*	95% CI†	Comments
Steenland and Brown [1995b], United States	Mortality study of 3,328 white male gold miners employed underground ≥ 1 yr between 1940 and 1965 and followed for mortality from 1977 to 1990. Mortality rates of U.S. males used for comparison.	Arthritis (ICD-9 categories 711–716, 720–721) (see comments)	17	2.19****	1.27–3.50	Study included all underlying and contributing causes of mortality after 1960 and other significant conditions documented on the death certificate.
	Other musculoskeletal disease as well as sclerosis, scleroderma, and lupus (ICD-9 categories 710, 717–719, 722–729, 731–739) (see comments)		10	2.14****	1.03–3.94	Statistically significant exposure-response trend ($P<0.05$) for chronic renal disease mortality and cumulative dust exposure.
	Nonmalignant skin diseases (ICD-9 categories 690–709) (see comments)		10	2.45****	1.17–4.51	
	Chronic renal disease in miners in highest cumulative dust exposure category (i.e., $\geq 48,000$ dust-days)		8	2.77****	1.20–5.47****	

*Odds ratio unless otherwise indicated.

†Abbreviations: Dash indicates not reported; AMG=alpha-1-microglobulin; BMG=beta-2-microglobulin; CI=confidence interval; NAG=beta-n-acetyl-D-glucosaminidase; OR=odds ratio.

‡None exposed.

§For history of silica dust exposure.

**Standardized incidence ratio (SIR).

††That is, caused by glomerulonephritis or interstitial nephritis.

‡‡Incidence (cases) per million black gold miners. Incidence in general population of black men of similar age (33–57) was 3.4 cases per million ($P<0.001$).

§§Disability cases.

****Rate ratio.

*****Receiving arthritis medication through national insurance plan.

****OR is for presence of silicosis.

§§§PMR.

****ICD-9 is the *International Classification of Diseases, 9th Revision* [WHO 1977].

****SMR.
****Reported in Steenland and Goldsmith [1995].

granulomas and hepatic silicosis [Kanta et al. 1986]. In workers exposed to crystalline silica, hepatic changes [Liu et al. 1991], hepatic or hepatosplenic silicosis [Clementsen et al. 1986; Oswald et al. 1995], and hepatocellular carcinoma [Clementsen et al. 1986] have been identified. Two studies reported a significantly higher proportion ($P<0.05$) of symptomatic hepatic porphyria (a chronic metabolic disease) in silica-exposed workers compared with control groups having no history of occupational silica exposure [Okrouhlík and Hykeš 1983; Zoubek and Kordac 1986]. However, the effect of silica on porphyrin synthesis and metabolism is not clear. In one study, alcohol consumption (quantity not specified) may have been a confounder [Okrouhlík and Hykeš 1983].

Mowry et al. [1991] reported a case of a cutaneous silica granuloma in a 57-year-old stonemason. Silica granulomas are firm, nontender dermal or subcutaneous nodules that usually appear at least several years (mean=10 years) after the exposure to silica. They may appear as a result of occupational exposure or trauma [Kuchemann and Holm 1979; Murphy et al. 1997] and are usually treated by excision. The mechanism that causes the silica crystals in the tissue to form a granuloma is unknown.

Cor pulmonale (enlargement of the right ventricle of the heart because of structural or functional abnormalities of the lungs) may occur as a complication of silicosis [Green and Vallyathan 1996] and other pneumoconioses [Kusiak et al. 1993a]. This condition is usually

preceded by pulmonary arterial hypertension. An epidemiologic case-control study of 732 white South African autopsied gold miners reported a statistically significant association ($P<0.05$) of cor pulmonale with "extensive" and "slight" silicosis [Murray et al. 1993].

Pulmonary alveolar proteinosis is a rare respiratory disease identified by an accumulation of phospholipid material in the alveoli [McCunney and Godefroi 1989]. Cases of this disease were identified in a U.S. cement truck driver [McCunney and Godefroi 1989], a U.S. sandblaster [Abraham and McEuen 1986], and a French ceramics worker [Roeslin et al. 1980]. Each worker had been potentially exposed to crystalline silica.

Skin absorption of crystalline and amorphous silica particles from soil, and subsequent obstructive lymphopathies related to the fibrogenic effects of the particles may be related to the development of nonfilarial tropical elephantiasis (podoconiosis) in the lower legs of residents of East Africa and certain volcanic areas [Frommel et al. 1993; Fyfe and Price 1985; Price and Henderson 1981].

Silica dust exposure may be associated with abrasion-related deterioration of dental health. Petersen and Henmar [1988] reported a 100% prevalence of dental abrasion in a group of 33 Danish granite workers. The authors recommended that dust concentrations be reduced, that workers wear face guards, and that dental abrasion from occupational dust exposure be considered an occupational disease.